Blanca Mompeo

José Sañudo

Arturo García-Touchard

New evaluation of human renal nerve anatomy provides key insights for distal renal specific denervation therapy for uncontrolled hypertension

Renal denervation is a treatment strategy for patients with uncontrolled systemic hypertension. The optimisation of the procedure is largely dependent on both the method of ablation used and the variation of the targeted nerves. Due to large variations in the renal nerve anatomy, re-evaluating the nerve patterns might significantly help optimise the therapy. *Confluence* spoke with Dr Blanca Mompeo of the University of Las Palmas, Gran Canaria, Professor José Sañudo of the Complutense University of Madrid and Dr Garcia-Touchard, interventional cardiologist at the Hospital Puerta De Hierro, Madrid, to discuss the rationale behind the gross anatomy study, and the impact that their findings will have on both the procedure of renal denervation and how renal anatomy is viewed.

What is renal denervation?

Dr Arturo García-Touchard (AG): Renal denervation (RDN) involves the ablation of both afferent and efferent renal sympathetic nerves with, for example, a radiofrequency-emitting catheter that is inserted percutaneously and sequentially into both renal arteries. Preliminary studies of RDN suggest that ablation of the sympathetic nerves leads to large reductions in blood pressure.[1,2] However, current use of the procedure is relatively limited, after results from the SYMPLICITY HTN-3 study failed to show significant reductions in hypertension with RDN in comparison to a sham procedure.[3] Despite this, many physicians still regard patients with truly uncontrolled arterial hypertension as good candidates for RDN.

Why did you think that it was important to take another look at renal anatomy?

Professor José Sañudo (JS): Gross anatomy is a topic that has been forgotten for many years, unfortunately. Towards the end of the 19th Century, the Spanish scientist, Santiago Ramón y Cajal, concluded that renal anatomy was already a well-established science and that the research required to discover any new significant findings would be extremely demanding. He therefore sent the following observation to his friend, Federico Oloriz, Professor of Anatomy at the Complutense University of Madrid:

Valencia, 3rd December 1896

Dear Federico Oloriz,

Descriptive anatomy is already an established science and in order to discover new details, extremely demanding long-term research is needed; however, normal histology, embryology, general physiology provides us with a large number of questions still to be answered. The field is so large and scarcely studied that, even if many men would dedicate their time to its study, many phenomena will remain undiscovered and hard work will be inherited by our successors.

Santiago Ramon y Cajal

[Arquiola E (1986) Gónzalez de Velasco reformador de los saberes morfológicos. Medicina e Historia 14(III):1-16]

Anatomical studies performed during the first half of the 20th century supported the hypothesis that severing the sympathetic fibres to the kidney via thoracic surgery might lead to improved control of hypertension.[4] However, this finding was only based on the painstaking work of dissections from a few authors and small samples of 12 or 14 cadavers at most. Within this same time period, other surgical procedures were developed and employed with the purpose of lowering blood pressure in patients

with severe uncontrolled hypertension. However, despite some documented improvement in blood pressure and morbidity, the surgical approach was largely abandoned due to surgical complications. Recent developments have led to an intravascular approach to treating hypertension via RDN.

Today, it is important that RDN continues to be rediscovered, as it provides another tool to control blood pressure. To advance our understanding of both renal nerve anatomy and RDN, we knew that we had to revisit the gross anatomy by dissecting human kidneys in a reliable sample of cadavers.

Dr Blanca Mompeo (BM): I agree with Professor Sañudo – the older observations of renal plexus anatomy in the 20th Century included some very beautiful studies, but assessing anatomy is at the centre of medical science, and studying the morphology is essential in all fields, especially with regards to RDN. Understanding the central anatomical substrata within each field of medicine is important; if we do not understand the anatomy, we are acting empirically rather than scientifically. This was our rationale behind conducting the gross anatomy study. This study was the first time that we studied the renal plexus and also the first time that a study applying micro-dissection to analyse the relationship between the nerves of the renal plexus and renal arteries in human cadavers has been published since the first part of the 20th century.

What was the gross anatomy study and how was it carried out?

JS: This study was a collaboration between multiple centres, which aimed to revisit the gross anatomy of the kidney and look at the anatomical relationships of the renal arteries and nerve supply.[5] My role in this study was as the head of the research group at the Complutense University in Madrid. Dr Mompeo visited my department to carry out the dissection of the cadavers and isolate the kidneys and renal nerves.

The first part of the study was focused around obtaining the cadavers and increasing the number of kidneys available. We ideally wanted to reach a confident number – towards 30 cadavers or so – which represents a value that we considered to be reliable enough to make some valid conclusions. So far, 12 cadavers, 6 male and 6 female, have been assessed, with more dissections performed since then.

The second stage was to isolate the kidneys and renal arteries, and perform histological procedures to observe the sections by microscopy. At the same time, specimens were transported to the hospital for computed tomography (CT) scans of matched histological sections. Using these CT sections, the next stage involved characterising the fibres along the renal arteries using immunohistochemistry.

How much variation in anatomy was observed between the cadavers?

JS: In the classic anatomy literature, there are plenty of comments about rare and strange findings, but variability is a common finding in the morphology of the normal body. We need to study reliable samples in order to identify meaningful anatomical patterns. There are many things still to be explained with regards to anatomy, but the idea that the human body is not only variable on the surface (the external appearance) but also internally, must be taken into account.

What did results of the study show?

JS: In the case of the sympathetic nerves of the kidneys, we have made a few key observations. The first is the existence of renal arteries that are not in the expected position. They often traverse from the aorta to the upper or lower poles of the kidney, not to the middle as expected. This anomaly was found in around 30% of study subjects.

BM: For me, this positioning of the nerve bundles of the renal plexus in relation to the renal artery was the most significant finding so far. In some papers we have seen that nerve bundles originating from the renal plexus were always located on the anterior or posterior face of the artery, in the adventitia of the arterial wall. Our study shows another common distribution; the main nerve bundles were in the superior and the inferior part of the renal artery – not in the adventitia, but around the artery. Furthermore, some of the renal plexus bundles led directly to the renal pelvis without closely following the segmental renal arteries.

JS: Yes, and this was another key finding: some nerve bundles went directly to the renal pelvis without direct close association with the arteries. When present, these direct nerve bundles followed the general path of the renal vasculature only along the distal quarter of the artery's length.

fig. 1

A) Anterior and B) posterior view of the renal sympathetic renal plexus of a right kidney.

Ag: adrenal gland

Arg: aorticorenal ganglion

Coe: coeliac ganglion

CoT: coeliac trunk

Ig: renal inferior ganglion

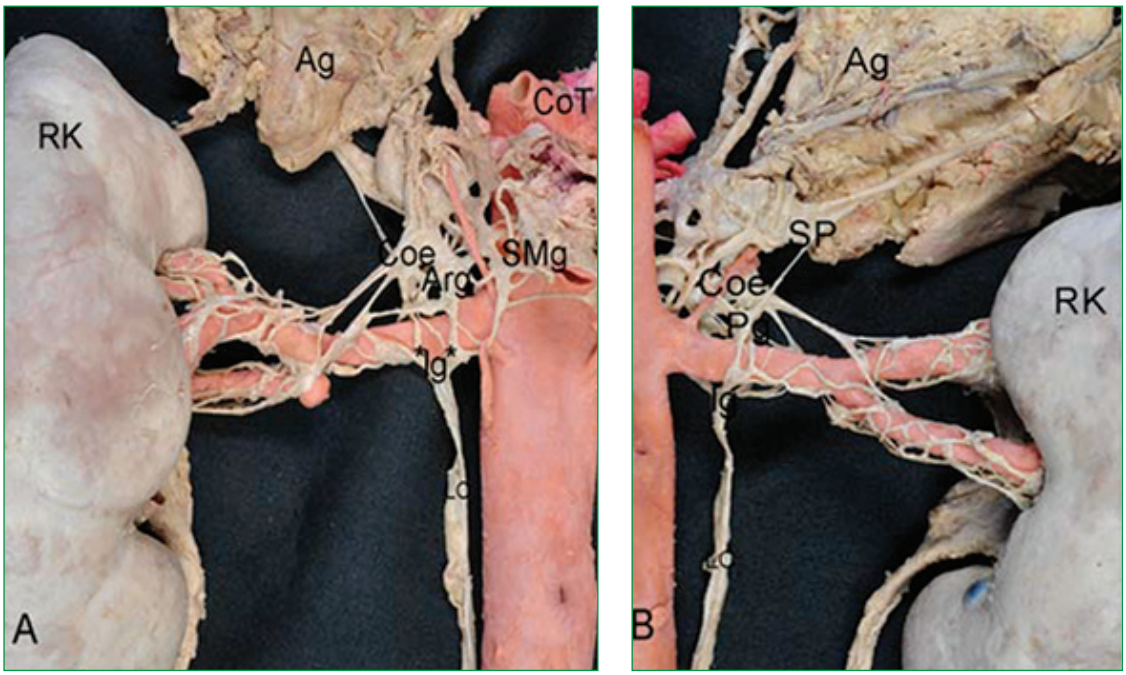
LC: contribution of the lumbar chain to the renal plexus

Pg: renal posterior ganglion

RK: right kidney

SMg: superior mesenteric ganglion

SP: Thoracic splanchnic nerves.



This is another common variation among individuals. We need to study this varying length of arteries and artery positioning, as the existence of upper nerve supplies poses interesting questions in clinical terms. However, the third and most interesting aspect we observed was a large ring of ganglia that occupied the area along the middle third of the renal artery and supplying nerve bundles to rest of the peritoneal and retroperitoneal anatomy.

BM: For me, I was especially surprised to see the ganglia form a ring around the proximal end of the renal artery, as this had not previously been described. The completed closed ring was observed in some cases, but not all. We expect to find this closed ring in the majority of cases, but more samples will need to be studied to conclude this.

We also observed small ganglia surrounding the arterial vessels beyond the main arterial bifurcation, although we currently do not know the nature of these ganglia. We could also see that there was some ganglionic growth, where some fibres coming from different origins could connect.

Based on your findings, would you recommend the ganglionic ring at the proximal end of the renal artery as a target for renal denervation?

JS: This is hard to say. If the ganglionic area has the most fibres going to the kidney and is the primary origin of these sympathetic fibres, it could be a good target in theory. However, with our results, there were probably 12–14% of cases where these fibres did not arise from the primary ganglionic ring, so this hypothesis may not apply to all people.

AG: This site would first require further investigation. The renal plexus is a completely unknown entity. We currently do not know if this ring could contain cross-over fibres going to other organs, which could make its use as a target site for ablation more high risk.

Do you think that your study may help us to better understand anatomical relationships between nerves and vasculature in other organ systems?

BM: As of yet, we do not know whether the relationship between the autonomic nervous system and the blood vessels is similar in every organ. From an anatomical point of view, the autonomic system has been poorly studied. Several authors from the first part of the 20th century studied these kinds of nerves in depth by dissection. In any case, I completely believe that our work may help to better understand the anatomical relationship between blood vessels and the autonomic nervous system, but the relationship would probably not be exactly the same in each organ.

What are the key findings from your study that cardiologists should take on board?

JS: First, it is important for cardiologists to check the arteriography of the entire aorta, not just the renal artery, and search for anatomical variations with accessory arteries before the procedure. The upper arteries could go to the upper or lower pole, so this needs to be confirmed. There are subjects that could have up to five arteries going to the kidney rather than just one, so the most important thing is to establish the arterial pattern of the kidney.

Cardiologists should also know that with any artery there are sympathetic nerves in the upper and lower surface interconnected by arborising bundles like a plexus, but the biggest are in the upper and lower aspects. If you remove these, there could potentially be a favourable effect. In summary, there are three key considerations: the arteriographic pattern, the position of the nerves around the arteries, as well as their variations, and the presence of nerve bundles originating in the upper part of the abdomen.

AG: For me, a key finding of our study is the variability found between cadavers with regard to the renal arteries, renal plexus, nerve bundles bypassing the renal arteries and the large ganglionic ring. This variability is visible not only from person to person, but also between each kidney found within the same individual. It is a very complex system that requires further investigation. Identifying small ganglia beyond the renal artery bifurcation was definitely another interesting find from this research, but we do not yet know the impact it may have in terms of our ability to control blood pressure.

Do you expect these results to change the clinical practice of RDN?

JS: From our work, I think that the field of RDN needs to increase focus on the research of arterial patterns and neural patterns, as well as the renal artery itself. I believe the procedure could be more effective if we better understood the anatomy, physiology and the histology. All of these factors could probably contribute to improving the quality of the therapy.

AG: In terms of the variability observed between the cadavers, we now know that finding a pattern that can simplify these differences is essential. By using patterns, we expect to able to modify the location of our target renal nerves to help optimise the efficacy of denervation. The variability we have found at the level of the renal arteries, nerves, ganglia and plexuses may explain why RDN only appears to be effective in some patients. As of yet, we do not know if this variation will impact the success of RDN when applied to the general population.

I have no doubt that the procedure works, and these findings will help to open up new lines of investigation. For RDN to be successfully adopted, we need additional studies like this to help improve knowledge of the target site and subsequently increase efficacy of the technique for a wider range of patients. The procedure needs to be simplified, so it may be the case that more than one catheter design is required to target multiple vessels beyond the main arterial bifurcation, and accommodate different sizes and angulations. From our findings specifically, moving forward it seems reasonable that the more distal we denervate, the more selective we will be, and thus less likely to impact other organs.

fig. 2

Symplicity Spyral™ Multi-electrode Renal Denervation Catheter

Address for correspondence
Dr Blanca Mompeo
Morphology Department
Health Sciences School
Las Palmas University
Gran Canaria, Spain

blanca.mompeo@ulpgc.es

+34 659 206 996

Professor José Sañudo
Department of Human
Anatomy and Embryology
Complutense University
of Madrid, Spain

jrsanudo@ucm.es

+34 696 489 022

Dr Arturo García-Touchard
Department of Cardiology
Hospital Puerta de Hierro
Autonomous University
of Madrid, Madrid, Spain

agtouchard@gmail.com

+34 627 994 899

Are there any follow-up investigations planned for this study?

BM: We are trying to increase the number of samples for our study. We need to perform more dissections, which will allow for statistical analyses. This will enable us to better understand details on the branches and how nerve bundle distribution can vary. We may also look for any variation between genders. Additionally, another important factor for further investigation is obtaining histological sections for immunohistochemistry, to detect the nature of the different nerve fibres and allow closer evaluation of the renal arteries. All other points would revolve around the practice of ablation, and a study in animal samples or maybe cadavers is something that we are considering.

Do you expect to observe anything new as you expand the study to include more cadavers?

BM: I am completely convinced that the pattern observed will be the same. I think that the distribution of the main bundles originating from the renal plexus will be the same, but we have only studied a part of the renal arteries. This is a study mainly focusing on nerves located before the bifurcation of the renal artery, so I think there is a lot of work to do. I am convinced that the ganglia ring could be the redistribution of the main branch of the renal plexus. I think that we need many more studies after the bifurcation of the renal artery and to see if we can more or less establish a pattern, depending on the variation of the renal arteries.

JS: I agree. My only expectations are to obtain more confident data and a more confident incidence in terms of nerve patterns and positions, to help to facilitate the management of the interventional devices when physicians carry out RDN. I hope that this study will contribute to having a more precise route for the procedures and more precise protocols in the future.

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DISCLOSURES: Nothing to disclose