THE ROLE OF ISCHEMIA IN THE DETERIORATION OF RENAL FUNCTION AFTER PARTIAL NEPHRECTOMY

Ricardo Arceo-Olaiz, Jose Manuel de la Morena, Virginia Hernandez and Carlos Llorente.


Summary.- OBJECTIVES: Nephron-sparing surgery (NSS) has been considered throughout history for patients with solitary kidney, bilateral renal tumors, impaired renal function (RF), and hereditary renal cancer. However, recently the indications for Partial Nephrectomy (PN) have extended and include patients with a healthy contralateral kidney. NSS has evolved in a great way during the last decade, specifically in terms of oncological indications, and in the renal ischemia time used with the goal to maintain as much renal function as possible.

This change is secondary to a better understanding of renal cancer histology, the equivalence in oncological outcomes between radical and PN, and finally the impact of chronic kidney disease (CKD) as a cause of cardiovascular complications and mortality.

The main purpose of our study is to review the role of ischemia in NSS.

METHODS: A literature review was performed focusing on NSS, risk factors of renal damage, types of ischemia, as well as its effect on RF, and ischemia time.

CONCLUSIONS: Renal ischemia has been considered for a long time as the main factor related with postoperative Renal Function (RF) in patients with NSS. Furthermore it is one of the few modifiable factors that directly depend on the surgeon. The ischemia time limit, both in warm and cold, is not well established and is a controversial issue that is still on debate till now. At this moment, there is evidence that considers the impact of ischemia only in acute or early stages. Also other factors have emerged and seem to have greater effect on RF, mainly in the long-term, leaving ischemia in second place. These factors are the quantity and quality of the remaining renal parenchyma. More studies are needed to support this rising concept and to clarify the real part that ischemia plays.

Keywords: Nephron-sparing surgery. Partial nephrectomy. Renal ischemia. Ischemia time. Renal function.

CORRESPONDENCE

Carlos Llorente
Hospital Universitario Fundación Alcorcón
Alcorcón. Madrid (Spain)
clorente@fhalcorcon.es

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Resumen.- OBJETIVO: Históricamente se ha considerado la Cirugía Renal Conservadora (CRC) en pacientes con riñón solitario, tumores bilaterales, alteración en la función renal y cáncer renal hereditario. Sin embargo en la actualidad las indicaciones de nefrectomía parcial se han extendido a pacientes con riñón contralateral sano. La CRC ha evolucionado de manera muy importante en la última década, específicamente en términos de indicaciones oncológicas y en el tiempo de isquemia.

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renal utilized with the objective of maintaining renal function.

The main purpose of our study is to review the role of ischemia in NSS.

METHODS

We performed a Medline literature research using the keywords partial nephrectomy, nephron sparing surgery, and ischemia. The articles were selected by one of the authors according to their importance and relevant content, remaining 41 for the review.

Risk Factors Related to Renal Damage in Nephron-Sparing Surgery

Although NSS has a protective effect on renal function (RF) compared to radical nephrectomy (RN), it is not free of inducing some level of renal dysfunction. There are different risk factors associated with renal damage after PN that have been described in previous literature. Such factors are classified as modifiable and non-modifiable depending on the surgeon’s intervention. The principal risk factors are ischemia in any of its forms, the amount of preserved renal parenchyma (PRP), preoperative glomerular filtration rate (GFR), the tumors’ characteristics, the patient’s age and comorbidities, the previous history of renal disease or surgery, and the complications derived from the surgery itself (5) (Table I).

In general when renal ischemia is mentioned, it is referred to WI. However there is another type which is used less frequently and is called cold ischemia (CI). Hypothermia has been established as an option in complex cases, since traditionally a WI longer than 30 minutes is recognized as harmful to kidney function (6). Hypothermia induces an interruption in renal metabolism, which is necessary to protect the cells and minimize postischemic renal injury. In clinical practice a temperature of 20 to

INTRODUCTION

Nephron-sparing surgery (NSS) has been considered throughout history for patients with solitary kidney, bilateral renal tumors, impaired renal function, and hereditary renal cancer. However, recently the indications for partial nephrectomy (PN) have extended and include patients with a healthy contralateral kidney. This can be explained by the fact that more than 50% of renal tumors are detected incidentally due to imaging indicated for a different reason (1). Additionally around 20 to 30% of renal incidentalomas either have a benign histology, or are low grade (2). PN is considered the standard of treatment for renal tumors < 7 cm (T1) when it is feasible according to the Clinical Guidelines of the European Association of Urology (3).

NSS has evolved in a great way during the last decade, specifically in terms of oncological indications. This change is secondary to a better understanding of renal cancer histology, the equivalence in oncological outcomes between radical and PN, and finally the impact of chronic kidney disease (CKD) as a cause of cardiovascular complications and mortality (4).
25°C apparently provides protection lasting up to 3 hours after vascular occlusion (7). Other authors have mentioned the safety of hypothermia with lower temperatures oscillating between 5 and 19°C (8).

Assessment of Renal Injury

Current literature shows that RN is an independent factor for developing CKD. Additionally, the latter relates directly with the risk of suffering cardiovascular disease and death because of it (1, 9, 10). Different studies have reported these results, and this is why PN is indicated in patients with normal contralateral kidney in whom it is feasible.

At first it was thought that PN did not have an effect on RF unlike RN as we mentioned earlier (11, 12). However, these studies used serum creatinine (SCR) as indicator of RF after NSS. This is an inaccurate marker since a normal value does not necessarily mean a normal RF, considering that the healthy contralateral kidney compensates for it and disguises the real function. A significant increase in SCR can be reflected when GFR declines around 30% from global RF (13). This is why it is mandatory to evaluate RF in both settings, ergo in patients with a solitary healthy kidney or with both healthy kidneys, as independent renal units.

Besides the use of SCR to measure RF before and after surgery, in patients with normal contralateral kidney, other more precise laboratory tests have been employed, such as 24 hr creatinine clearance (CC) and some other markers of renal damage. CC is a lot more accurate compared to SCR, nevertheless it has the disadvantage that it exclusively reflects global RF and cannot differentiate each renal unit’s contribution. Some centers have studied different biomarkers in order to evaluate their impact and prediction of acute renal injury. Some of them are alanine aminopeptidase, lysozyme, gamma-glutamyl transpeptidase, and pro-atrial natriuretic peptide (14, 15). Results so far have not considered these markers useful in clinical practice, and their role must be established.

Image studies, especially nuclear medicine tests, have been of great utility in the evaluation of global RF when it comes to determine each kidney’s contribution to RF. Porpiglia et al studied the effect of WI by different methods in patients with laparoscopic partial nephrectomy (LPN). They used tubular enzymes, SCR, CC renogram with EDTA for global RF and with MAG3 to assess the effect on the operated kidney. Their conclusions were: 1) tubular enzymes are not good markers for renal damage; 2) proteinuria indicates injury, but it does not measure it; 3) renogram with EDTA does not detect significant changes in RF; and 4) the RF of the operated kidney decreases immediately after surgery, but recovers one year after the procedure without reaching its basal function (14). They also reported in a more recent study the long-term impact on RF in the same group of patients four years after the surgery (16). In this update they only used SCr, CC, and MAG3 renogram to measure postoperative RF. They found that SCr and their derivates such as CC, have a low sensitivity for evaluation of RF, supporting their previous outcomes. They suggest that the correct method to assess RF in this setting is the renogram, with the maximum impact 3 months after surgery and thereafter with some recovery, but without reaching the basal status. So far this is the study with the longest follow-up in terms of RF in patients with LPN.

Funahashi et al assessed the extension of ischemic injury in patients with NSS by three different methods: effective renal plasma flow (ERPF), calculated from 99mTc-MAG3 scintigraphy, renal parenchymal volume (RPV) calculated by CT images, and regional 99mTc-MAG3 uptake in surgically non-affected parts (17). They found that to longer periods of ischemia, there are less ERPF and RPV. Contrary to what Porpiglia reported, patients with ischemia shorter than 25 minutes reached their basal RF 6 months after PN. They suggest that CT represents mainly remaining renal tissue volume, which at the same time can be affected by ischemic injury. Nevertheless, CT cannot clarify which region was damaged secondary to the ischemia. Instead MAG3 scintigraphy is a lot more precise, even to differentiate parts with no affection secondary to surgery.

Recent studies assess RF before and after PN with nuclear medicine tests. However variability exists when it comes to which radioisotope they use. Choi et al, contrary to previous reports, evaluated ischemic damage in patients with LPN and robot-assisted partial nephrectomy (RAPN) with DTPA renogram instead of MAG3 (18). This group confirmed what as previously mentioned by Funahashi, when a longer period of ischemia is present, there is a notorious decrease in GFR. On the other hand, they did not observe differences in regional enhancement of healthy tissue adjacent to the surgical site. This finding contradicts what other studies have reported (17), and guides us to think that it could be secondary to the radioactive tracer used. Which is the right radioisotope to quantify GFR either as global RF or as renal unit? Some authors consider DTPA gammagraphy the standard to measure GFR independently of the SCR value (19). Others mention that nowadays MAG3 scintigraphy for estimating function of separate renal units is the most exact method available in the setting of RF loss after tissue resection and ischemic injury (20). Which
radioactive tracer to choose is still a controversial issue in our time.

**Mechanisms of Renal Damage Secondary to Ischemia and Types of Ischemia**

Renal hilum clamping is a very important part of PN surgical technique. This step has different advantages which are well known, such as a decrease in hemorrhage, better visualization of the surgical site, and evaluation of surgical margins, as well as the possibility of carrying out hemostasis a lot faster (17). Nevertheless, all these elements in favor of clamping must be weighed against the fact that occlusion of renal blood vessels has the risk of provoking an ischemic injury.

The mechanism secondary to renal ischemia occurs mainly at vascular level, provoking obstruction of the vessel and a reperfusion lesion, which at the same time decreases renal blood flow and consequently lowers the organ’s activity (21). There is a very important inflammatory response in the blood vessels which is derived from interleukin release and produces vasoconstriction. A vicious circle is activated due to endothelial damage provoked by activation of a cytokine cascade with the following arteriolar vasoconstriction. The secondary low renal flow liberates angiotensin II. Simultaneously there is a breakdown in oxidative phosphorylation and adenosine triphosphate (ATP), which provokes cell swelling due to water passive diffusion. The ATP that is able to degrade, triggers free radical liberation which induces additional damage, and is well known as reperfusion injury (6, 22).

There are two types of ischemia, warm and cold, being the former the most commonly used around the world. In the same way that happens with WI, the correct time to decide when to use cold technique is controversial. This is secondary to the fact that, as we mentioned earlier, the time threshold by which ischemic injury causes kidney functional damage is not well known and therefore the exact time to act is a very complicated decision.

There are different forms of hypothermia that have been used in both open and laparoscopic NSS. The cooling of the kidney by direct ice slush is considered the gold standard (7). Another option is arterial infusion of hypothermic solution by femoral arterial occlusion by itself in order to obtain this “venous protector effect”. Its weaknesses are an inadequate decline in cortical temperature, concentrating hypothermia in the central part of the kidney (24). Back-table surgery with autotransplantation has also been described. These days this technique has been mostly abandoned, nonetheless it is considered a last resource with good outcomes in extremely complex cases (25).

Lane BR performed a study to compare the effects of warm and CI in solitary kidney patients (5). He found that patients with CI were older, with a lower basal GFR, and with a higher incidence of CKD. However a significant difference was not observed in GFR meaning a decrease in both postoperatively and in the long-term for the two forms of ischemia. He mentions that CI had a protector effect that showed functional results similar to WI, despite longer periods of ischemia. The perfect setting encompasses a surgeon that can anticipate and evaluate which cases will need a prolonged WI and establish promptly a hypothermic technique to diminish postsischemic renal injury.

There are two ways to accomplish renal vessels clamping at the time of resecting a tumor. Either only the artery is clamped, or enbloc occlusion is performed in order to stop both venous and arterial flow. The latter is done more frequently in LPN. It has been suggested that when only arterial flow is suspended, there is partial oxygenation effect caused by retrograde venous flow. However its disadvantage is a rise in venous intraoperative bleeding risk and worse surgical site visibility (21). Imbeault A et al carried out a study in subjects with LPN and divided them in two groups to assess arterial clamping (AC) compared to arterial and vein (AV) (26). Clamping time, and therefore WI time, was significantly higher in patients with AC compared to AV. Regarding long-term RF, there were no significant differences between both groups, which suggests that it is not necessary arterial occlusion by itself in order to obtain this “venous protector effect”.

**Impact of Ischemia on Renal Function**

The initial studies that evaluated WI were experimental and performed in human kidneys in the 80’s. One of the most important mentions that a warm ischemia time (WIT) less than 10 minutes does not cause damage; when 30 minutes are reached the damage is reversible; after 30 minutes there is risk of irreversible damage; and when ischemia is longer than 60 minutes, the injury produced is irreversible (27). With these results, tubular degeneration was demonstrated and begins after 20 to 30 minutes after hilar clamping. This is why the limit or threshold
of 30 minutes of WIT has been adopted around the world.

Other studies with different techniques, such as open partial nephrectomy (OPN), LPN, and RAPN, followed with the goal to confirm or establish a new ischemia threshold. More recent evidence suggests that WI optimal length is 20 minutes, although some authors consider a 30 minutes threshold (20, 28, 29). Thompson RH et al performed a study in patients with a solitary kidney and operated by NSS and found that WIT longer than 20 minutes is associated with a higher risk of suffering acute renal failure (ARF) and CKD (30). These results show a more certain view because assessing subjects with solitary kidney unmask authentic evidence and brings us closer to reality. In a more recent study they updated their results now in 362 patients (31). This report is the largest series of solitary kidney patients so far. Contrary to their previous study, they found significant differences with longer WIT, being the limit in this occasion 25 minutes. However they proved that every minute of ischemia has a significant impact on RF in both its manifestations as ARF or CKD. They quantified the risk of each WI minute and showed that it confers a 5% risk of suffering ARF and 6% of CKD stage IV.

Nguyen MM and Gill IS described a technique which they called “early unclamping” of the renal hilum (32). They evaluated 100 consecutive patients operated by LPN and divided them into two groups. The first one included patients with regular LPN and the second group the ones with early unclamping, which consists of using exclusively WI during the initial suture of the renal parenchyma and stopping it for the remaining repair. With this technique they achieved to reduce significantly in more that 50% WIT from 31.1 to 13.9 minutes. Furthermore no significant differences were documented in terms of complications among both groups.

Later on, this same group continued perfecting their technique until they accomplished what they called “zero ischemia anatomic partial nephrectomy” (33). This approach was carried out by laparoscopy or robot-assisted techniques and consists of selective anatomic vascular microdissection of tumor specific arterial branches, specifically tertiary, quaternary or higher order. They achieved adequate RF preservation with the same amount of complications as in other series. Nonetheless they had a high transfusion rate of 19.3%. The authors conclude that this technique is feasible, even for complex tumors, and eliminates the most important factor that depends directly from the surgeon, which is ischemia time. This study was criticized due to the great number of transfusions because it does not correlate with the bleeding reported during surgery or postoperatively (34). The editorial also mentions that it is really important to consider judiciously the fact of avoiding the use of ischemia instead of performing a very careful surgical technique and try to preserve as most renal parenchyma as possible.

Everyone is attempting to lower WIT with the aim of maintaining as much RF as possible. However the longest WIT time is not well known. As a matter of fact, this controversial issue is still a matter of debate. Table II depicts different NSS series and WIT limits which affect RF.

Table I. Risk factors associated with renal damage after NSS.

<table>
<thead>
<tr>
<th>Non modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Amount of PRP</td>
<td>- Ischemia</td>
</tr>
<tr>
<td>- Preoperative GFR</td>
<td>- Warm</td>
</tr>
<tr>
<td></td>
<td>- Cold</td>
</tr>
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<td></td>
<td>- Postoperative complications</td>
</tr>
</tbody>
</table>

Tumor characteristics

- Size
- Location
- Age
- Comorbidities
- Previous renal surgery or disease
Despite WI is considered to be the main factor related to postoperative RF in NSS, recent literature has assessed other parameters which seem to have a greater impact on the kidney in the long-term. These parameters are related with the quality and quantity of residual renal parenchyma after NSS (5). Simmons MN et al developed a mathematical method which uses CT in order to estimate the PRP functional volume percentage (36). They applied this model in 39 patients and found that volume loss is closely related to long-term RF. Afterwards they assessed ischemia and percent functional volume preservation (PFVP) in 301 subjects, both in the short and in the long-term (37). They found that both ischemia and residual volume (depicted by PFVP) had a significant effect over GFR immediately after the surgery. Nevertheless during long-term follow-up with a mean time of 1.4 years, only volume loss had a significant impact over RF. This finding questions the fact that ischemia is the principal factor related to RF in patients operated of NSS. This could change the perception that exists about ischemia and RF and lead us towards a new objective, which is greater renal parenchyma preservation in this group of patients.

NSS produces injury, which has variable magnitude with the following decline in GFR. This effect over GFR seems to depend on 3 main factors: 1) functional volume loss, 2) acute renal injury related to ischemia, and 3) mechanical effects due to trauma. At the same time, volume loss happens as consequence of resected healthy tissue adjacent to the renal tumor, as well as collateral damage secondary to renorraphy and tissue remodeling (37). The recovery phase presents during the following months after the surgery. During this stage, trauma effects and ischemia are reverted until a new basal function is reached depending on the amount of residual functional kidney parenchyma.

Thompson RH et al performed a study to assess the influence of quality and quantity of renal tissue on RF in patients with NSS (38). The quantity was measured by PRP mean percentage, and quality by preoperative GFR. They found that WI is exclusively related to ARF and not with long-term RF, just as Simmons MN did. Both preoperative GFR and preserved kidney percentage had a significant effect over RF in the short and long terms. These outcomes confirm what other authors mentioned before and validate the fact that adequate quantity and quality tissue seem to be more important than ischemia time during NSS.

The Use of Mannitol During Renal Ischemia

Mannitol is an osmotic diuretic that has been traditionally used in kidney surgery to lower the risk of perioperative renal failure. Supposedly it increases renal blood flow by means of decreasing intravascular cellular inflammation, free radical scavenging, and renin production, as well as increase of intravascular volume. This limits the effect of hypoxia and ischemic injury (39).

Different studies have reported a beneficial effect in terms of reperfusion (40). These studies were carried out in animals and in the field of renal transplantation. Nowadays it is considered that this evidence is scarce, and the potential effect of mannitol could be non-existent or even harmful for RF. In the setting of NSS, a study was performed and assessed the effect of perioperative use of mannitol on RF in

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Surgery</th>
<th>WIT limit (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porpiglia F (14)</td>
<td>18</td>
<td>NPL</td>
<td>32</td>
</tr>
<tr>
<td>Choi JD (35)</td>
<td>37</td>
<td>NPL/NPAR</td>
<td>28</td>
</tr>
<tr>
<td>Funahashi Y (17)</td>
<td>32</td>
<td>NPA/NPL</td>
<td>25</td>
</tr>
<tr>
<td>Thompson RH (30)</td>
<td>174</td>
<td>NPA</td>
<td>20</td>
</tr>
<tr>
<td>Nguyen MM (32)</td>
<td>100</td>
<td>NPL</td>
<td>13.9</td>
</tr>
<tr>
<td>Thompson RH (31)</td>
<td>362</td>
<td>NPA</td>
<td>1</td>
</tr>
<tr>
<td>Gill (33)</td>
<td>58</td>
<td>NPL/NPAR</td>
<td>0</td>
</tr>
</tbody>
</table>
the long-term in subjects with minimally invasive PN (41). The patients were divided in two groups. In the first one, mannitol was given during surgery, and in the second mannitol was not used. The results showed that the fact of using mannitol during surgery was not associated with a better postoperative RF.

The evidence level is low when it comes to the use of mannitol as RF protector, and randomized trials to evaluate if this diuretic has a significant impact in the long-term in patients with NSS are needed. So far there is not enough evidence to support or disqualify the use of mannitol in PN.

**CONCLUSIONS**

Most of the studies published in the literature are retrospective and include a limited number of patients. It is important to take this into consideration at the time of analyzing the results. Renal ischemia has been considered for a long time as the main factor related with postoperative RF in patients with NSS. Furthermore it is one of the few modifiable factors that directly depends on the surgeon. The ischemia time limit, both in warm and cold, is not well established and is a controversial issue that is still on debate till now. At this moment, there is evidence that considers the impact of ischemia only in acute or early stages. Also other factors have emerged and seem to have greater effect on RF, mainly in the long-term, leaving ischemia in second place. These factors are the quantity and quality of the remaining renal parenchyma. More studies are needed to support this rising concept and to clarify the real part that ischemia plays.

**REFERENCES AND RECOMMENDED READINGS**

(*of special interest, **of outstanding interest)

18. Choi JD, Park JW, Kim HS, Jeong BC, Jeon SS,


