Acute Kidney Injury Induced by Pneumoperitoneum Pressure Via a Mitochondrial Injury-dependent Mechanism in a Rabbit Model of Different Degrees of Hydronephrosis

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OBJECTIVE To clarify the effect of mitochondrial injury during laparoscopic surgery of the kidney in different degrees of hydronephrosis in rabbit model.

METHODS A total of 90 rabbits were randomly allocated into 3 groups (groups PN, PM, and PS, ie, rabbits without, with mild and with severe hydronephrosis, respectively). The rabbits in the PM group (n = 30) and PS group (n = 30) underwent surgical procedures that induced mild and severe left hydronephrosis, respectively. The rabbits in all the groups were then allocated into 5 subgroups and were subjected to intra-abdominal pressures of 0, 6, 9, 12, and 15 mmHg. Changes in the mitochondrial membrane potential and mitochondrial electron microstructure were observed. The apoptosis proteins cytochrome C, apoptosis-inducing factor, caspase-3, and caspase-9 were measured by western blot analysis.

RESULTS As the degrees of hydronephrosis increased, histopathological changes such as the decrease in mitochondrial membrane potential and mitochondrial vacuolization along with increased expression of apoptosis proteins, cytochrome C, apoptosis-inducing factor, caspase-3 gained statistically significance at lower intra-abdominal pressures (In PN and PM groups at 15 mmHg, and in PS group at 9 mmHg; for all $P < .01$).

CONCLUSION Mitochondrial injury plays an important role during acute kidney injury induced by pneumoperitoneal pressure in different degrees of hydronephrosis in the rabbit model. UROLOGY 127: 134.e1–134.e7, 2019. © 2019 Published by Elsevier Inc.

Minimally-invasive surgery using carbon dioxide pneumoperitoneum has become a popular surgical method in the fields of urology, hepatology, gastroenterology, and gynecology. The method is associated with shorter hospitalization, reduced postoperative pain, and minimal scar tissue, making the approach appealing to patients.[1-3] A certain degree of pneumoperitoneum pressure is needed during the laparoscopic surgery process. The kidneys could suffer an injury as the pneumoperitoneum pressure compresses the renal parenchymal and renal veins.[4-6] The risk of this injury increases when the kidneys have hydronephrosis. Our previous study in rabbits demonstrated that kidneys with severe hydronephrosis were more likely to suffer from acute kidney injury when they were exposed to pneumoperitoneum pressure than those with mild hydronephrosis.[7] To sustain their normal function, the kidneys use a large amount of energy. Mitochondria are dynamic subcellular organelles with critical roles in energy generation, and mitochondrial dysfunction can induce kidney injuries. This study aimed to assess the effects of mitochondrial injury on acute kidney injury induced by pneumoperitoneum pressure using the same rabbit model we reported on previously.

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Compliance with Ethical Standards: *Approval was obtained for this study from the ethics Committee of Wuhan University. We have considered the ethical issues involved in this research and believe that we have adequately addressed them in this application. We understand that if the protocol for this research changes in any way we must inform the Research Ethics Review Committee.*

Ethical approval: *Our study protocol was approved by the institutional review board of Wuhan University. Animal care and treatment were conducted in accordance with the National Institutes of Health Guidelines for ethical animal research. The Animal approved project number is: 00092583.*

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MATERIALS AND METHODS

Animals and Groups

A total of 90 adolescent male New Zealand rabbits weighing 2.0-2.5 kg were purchased from animal experiment center of Wuhan University (Wuhan, China). The rabbits were housed in a standard animal room. Light was set up with 12-hour on/off and standard food and water were provided. All procedures were approved by the Animal Ethics Committee of Wuhan University. The study was conducted according to the rules and requirements for an animal laboratory study, as determined by the committee.

The rabbits were randomly divided into a control group and 2 experimental groups, as in our previous study.[7] Briefly, the experimental group rabbits underwent a surgical operation to create either mild hydronephrosis (PM group) or severe hydronephrosis (PS group).[8] The rabbits from each experimental group were then divided into 5 subgroups (PM0-PM4 and PS0-PS4) that were each composed of 6 rabbits. The rabbits in groups 0-4 of each experimental group had carbon dioxide infused into their abdomens to keep an intra-abdominal pressure of 0, 6, 9, 12, or 15 mmHg, respectively. For the control group (group PN), no surgical operation was performed, and the rabbits were directly divided into 5 subgroups (PN0-PN4) that were each composed of 6 rabbits. The rabbits in the PN0-PN4 groups had carbon dioxide infused into their abdomens to achieve an intra-abdominal pressure of 0, 6, 9, 12, or 15 mmHg, respectively. Acute kidney injuries that arose from mitochondrial injury were evaluated using changes in mitochondrial membrane potential (MMP), mitochondrial electron microstructure, and the expression levels of apoptosis proteins, such as cytochrome C (Cyt-C), apoptosis-inducing factor (AIF), caspase-3, and caspase-9.

SURGICAL OPERATION

We manipulated the model as previously described by Wen.[8] Briefly, the rabbits were first anesthetized with sodium pentobarbital (30 mg/kg) (Kyoritsu Seiyaku, Tokyo, Japan). The psoas muscle, left ureter, and left lumbar vein were exposed by a left lower abdominal incision. For the PM group, the upper ureter was buried in a 2.5 cm notch within the psoas muscle. The muscle edge was then sutured over the ureter. For the PS group, a same manipulation was performed in a 6 cm notch within the muscle. The abdomen was then sutured back together. Two weeks later, B-ultrasonography was used to confirm the hydronephrosis model. In the PN group, the thicknesses of parenchyma were 0.36 ± 0.03 cm and no calices distention was observed. In the PM group, the thicknesses of the parenchyma and calices distention were 0.33 ± 0.09 cm and 0.95 ± 0.27 cm, respectively ($P < .001$ compared with PN groups). In the PS group, they were 0.22 ± 0.05 cm and 1.70 ± 0.34 cm, respectively ($P < .001$ compared with PN groups). The differences between the 2 thicknesses were significant in both the mild and severe groups. A second operation was then performed when the hydronephrosis models were confirmed. After the rabbits were anesthetized, a 0.3 cm long aperture was made in the left abdomen. A 10-gauge veress needle (Johnson & Johnson, New Jersey, USA) was inserted into the abdominal cavity through the aperture, and the other side of the needle was connected to a CO_2 insufflator (Stryker Endoscopy, Kalamazoo, MI). Before insufflation, the gap around the needle was sutured to prevent CO_2 leakage. The pressure for subgroups 0-4 was set at 0, 6, 9, 12, and 15 mmHg, respectively, for the PN, PM, and PS groups. After 1 hour of insufflation, the pneumoperitoneum was released, and the animals were induced to recover for 12 hours. At the end of each experiment, the rabbits were sacrificed through an intravenous overdose injection of pentobarbital sodium, and their left kidneys were harvested for the evaluation of mitochondrial injuries.

Mitochondrial Membrane Potential (MMP) Detection

The MMP was determined using 5,5', 6,6'-tetrachloro-1,1', 3,3'-tetraethyl-imidacarbocyanine iodide (JC-1, Beyotime Institute of Biotechnology, Jiangsu, China). Briefly, renal tissue was digested in a trypsin-EDTA solution (Beyotime Institute of Biotechnology, Jiangsu, China), and the digestion was terminated by adding bovine serum. Suspension cells were harvested and loaded with 1 × JC-1 at 37°C for 20 minutes, and then the cells were washed and analyzed by flow cytometry (FACS Aria III, BD, NJ). When the MMP levels are low, JC-1 exists mainly as a monomer, which emits green fluorescence (with an excitation wavelength of 490 nm and emission wavelength of 530 nm). When the MMP levels are high, JC-1 exists mainly as a polymer, which emits red fluorescence (with an excitation wavelength of 525 nm and emission wavelength of 590 nm). The value of the MMP was expressed as the ratio of red fluorescence intensity to green fluorescence intensity.

Renal Tissue Mitochondrial Ultrastructure Evaluation

The dissected tissues were fixed with 2.5% glutaraldehyde, rinsed 3 times in 0.1M phosphate buffer, postfixed in 1% buffered osmium tetroxide and then rinsed in 0.1M phosphate buffer. Subsequently, the tissues were dehydrated by incubation ingraded alcohol, and then the dehydrated tissues were embedded in epoxy resin. Thin tissue sections were cut using an ultramicrotome (LKB, Bromma, Kista, Sweden) and stained with uranyl acetate and lead citrate. Mitochondrial ultrastructural changes were observed and photographed using a transmission electron microscope (H-600, Hitachi, Tokyo, Japan).

Evaluation of the Expression Levels of Apoptosis Proteins

The renal tissues were digested by tissue lysate buffer (Beyotime Institute of Biotechnology, Jiangsu, China). The concentration of the total protein was quantified by the bicinchoninic acid method using a kit (Beyotime Institute of Biotechnology, Jiangsu, China). Ten micrograms of total protein from each sample was loaded on a sodium sulfate (SDS)/polyacrylamide electrophoresis gel, and the proteins were transferred to a polyvinylidene fluoride membrane (Millipore, USA). The membranes were

then blocked by incubation in Tris-buffered saline Tween (TBS and 0.1% Tween 20) containing 5% bovine serum albumin and were subsequently exposed to primary antibodies specific to Cyt-C (R&D systems, Minnesota, USA), AIF (R&D systems, Minnesota, USA), caspase-3 (Santa Cruz Biotechnology, California, USA) or caspase-9 (Santa Cruz Biotechnology, California, USA) in a humidified chamber at 4°C overnight. Then, the membranes were incubated with a fluorescent secondary antibody (LI-CRO Biosciences, NE). After washing with Tris-buffered saline Tween, the membranes were scanned using an Odyssey System (LI-COR Biotechnology, Nebraska, USA).

Statistical Analysis

All the values are expressed as the mean ± SEM. Statistical analyses were performed using SPSS 17.0 software. One-way analysis of variance and Tukey's test were used for statistical comparisons. $P < .05$ was used to indicate statistical significance.

RESULTS

MMP Levels After Intra-abdominal Insufflation

A decrease in MMP levels was considered to be an indicator of early apoptosis. To better assess the MMP levels in the kidneys subjected to intra-abdominal pressure, the MMP was measured using flow cytometry and JC-1 staining. The MMP level is expressed as the ratio of red fluorescence (JC-1 polymer) to green fluorescence (JC-1 monomer). A decrease in the ratio represents a decrease in the MMP level. Figure 1A shows the red fluorescence (Q2) and green fluorescence (Q4) of the renal cells that were exposed to intra-abdominal pressure, as determined by flow cytometry. The red fluorescence increased while the green fluorescence decreased as the intra-abdominal pressure increased (Fig. 1A). In the PN group, the MMP levels at 0, 6, 9, and 12 mmHg ($P > .05$) were similar, but they were significantly decreased at 15 mmHg ($P < .05$; Fig. 1B). In the PM group, the MMP levels were similar at 0, 6, 9, and 12 mmHg ($P > .05$), but they were significantly decreased at 15 mmHg ($P < .05$; Fig. 1B). In the PS group, the MMP levels were similar at 0 and 6 mmHg, but they were decreased at 9, 12, and 15 mmHg ($P < .05$; Fig. 1B).No significant differences were observed among the subgroups PS2, PS3, and PS4 ($P > .05$; Fig. 1B).

Changes in Mitochondrial Ultrastructure

To observe mitochondrial damage that was stimulated by the intra-abdominal pressure in renal tubular cells, the percentage of swollen and vacuolar mitochondria was calculated in 5 random fields of each slide. Figure 2A shows the swollen and vacuolar mitochondria of renal cells that were exposed to intra-abdominal pressure. The number of swollen and vacuolar mitochondria increased at specific pressure levels as the intra-abdominal pressure increased (at 15 mmHg, 15 mmHg, and 9 mmHg, respectively, in the PN, PM, and PS groups; Fig. 2A). In the PN group, the percentage of swollen and vacuolar mitochondria was similar at 0, 6, 9, and 12 mmHg ($P > .05$), but it was significantly increased at 15 mmHg (40.00 ± 8.10%, $P < .05$; Fig. 2B). In the PM group, the percentage of swollen and vacuolar mitochondria was similar at 0, 6, 9, and 12 mmHg ($P > .05$), but it was significantly increased at 15 mmHg (44.33 ± 8.76%, $P < .05$; Fig. 2B). In the PS group, the percentage of swollen and vacuolar mitochondria was similar at 0 and 6 mmHg, but it was increased at 9, 12, and 15 mmHg (52.00 ± 11.63%, 46.33 ± 8.98, and 48.33 ± 9.11%, respectively, $P < .05$; Fig. 2B). No significant differences were observed among the subgroups PS2, PS3, and PS4 ($P > .05$; Fig. 2B).

Expression of Apoptosis Proteins

We investigated whether the apoptosis proteins Cyt-C, AIF, caspase-3, and caspase-9 were associated with mitochondrial damage as the kidneys were subjected to elevated intra-abdominal pressure. Western blot analysis revealed that Cyt-C, AIF, caspase-3, and caspase-9 levels were similar at 0, 6, 9, and 12 mmHg ($P > .05$), but they were significantly increased at 15 mmHg ($P < .05$; Fig. 3) in the PN group. In the PM group, Cyt-C, AIF, caspase-3, and caspase-9 levels were similar at 0, 6, 9, and 12 mmHg ($P > .05$), but they were significantly increased at 15 mmHg ($P < .05$; Fig. 3). In the PS group, Cyt-C, AIF, caspase-3, and caspase-9 were similar at 0 and 6 mmHg, but they were increased at 9, 12, and 15 mmHg ($P < .05$; Fig. 2B). No significant differences were observed among the subgroups PS2, PS3, and PS4 ($P > .05$; Fig. 3).

DISCUSSION

Our previous study showed that acute kidney injury occurred when intra-abdominal pressure was elevated to a certain threshold during pneumoperitoneum. We also discovered that this injury occurred more easily in obstructed kidneys.[7]

We first observed that mitochondrial damage resulted from elevated intra-abdominal pressure during the limited surgery operation time. We speculated that the injury was induced by mitochondrial dysfunction. The kidneys are highly aerobic organs. They receive approximately 1/4 of the cardiac output and are densely populated with mitochondria, which are required to produce enough energy, including ATP, to re-uptake over 98% of the filtered load.[9]

ATP generation in the mitochondria relies on the aerobic respiratory chain, and MMP plays an important role in the chain. The MMP assists electron transmission, prompts the combination of O_2 and H^+, and contributes to the generation of ATP.[10-12] Hypoxia decreases MMP stability, thereby disrupting ATP generation and inducing the opening of the mitochondrial permeability transition pore.[13] Along with the opening of the mitochondrial permeability transition pore, ATP is depleted by the mitochondrial uncoupling of the oxidative phosphorylation system, which induces the influx of small molecules into the mitochondria. This influx of small molecules causes mitochondrial swellen and vacuolate, and soon after, mitochondrial spilled and the released some apoptotic proteins such as Cyt-C from the mitochondria, wihch finally leaded to cell death.[14,15] Wiesenthal et al reported that an elevated intra-abdominal pressure secondary to pneumoperitoneum caused significant renal hypoxia and decreased renal blood flow.[16] In this study, we observed that in both the normal and mild hydronephrosis groups,

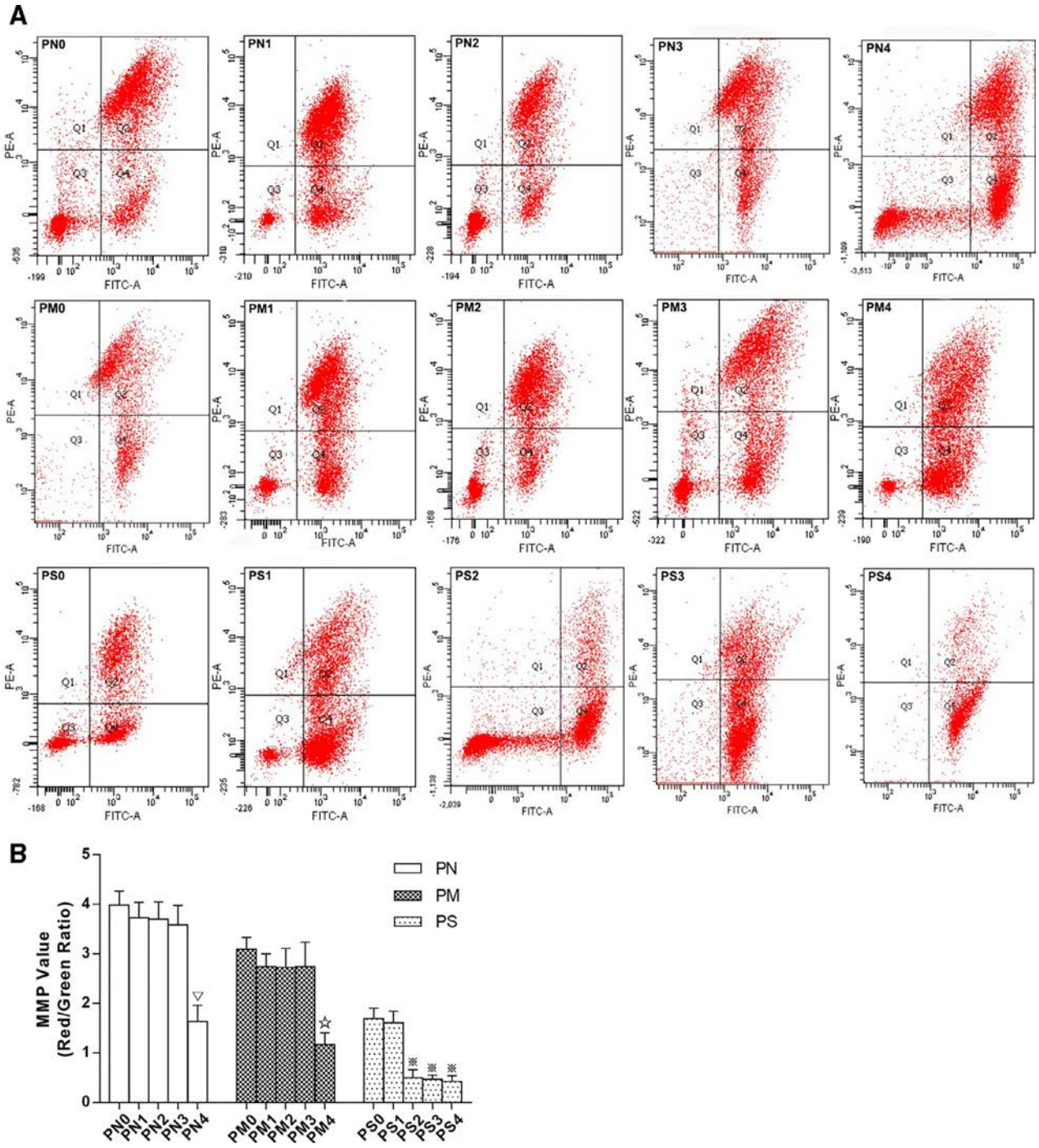

Figure 1. The mitochondrial membrane potential (MMP) of renal cells that were subjected to different amounts of intra-abdominal pressure in mild and severe hydronephrosis. PE-A represents red fluorescence, and FITC-A represents green fluorescence. The MMP values were expressed as the ratio of red fluorescence intensity (Q2) to green fluorescence intensity (Q4). (**A**) MMP analysis by flow cytometry in rabbits with normal, mild, and severe hydronephrosis. (**B**)MMP value of renal cells in normal, mild, and severe hydronephrosis. PN0, PN1, PN2, PN3, and PN4 represent normal rabbits that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. PM0, PM1, PM2, PM3, and PM4 represent rabbits with mild hydronephrosis that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. PS0, PS1, PS2, PS3, and PS4 represent rabbits with severe hydronephrosis that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. $^{\triangledown}P < .05$, compared with the PN0 group. $^{\star}P < .05$, compared with the PM0 group. $^{\divideontimes}P < .05$, compared with the PS0 group.

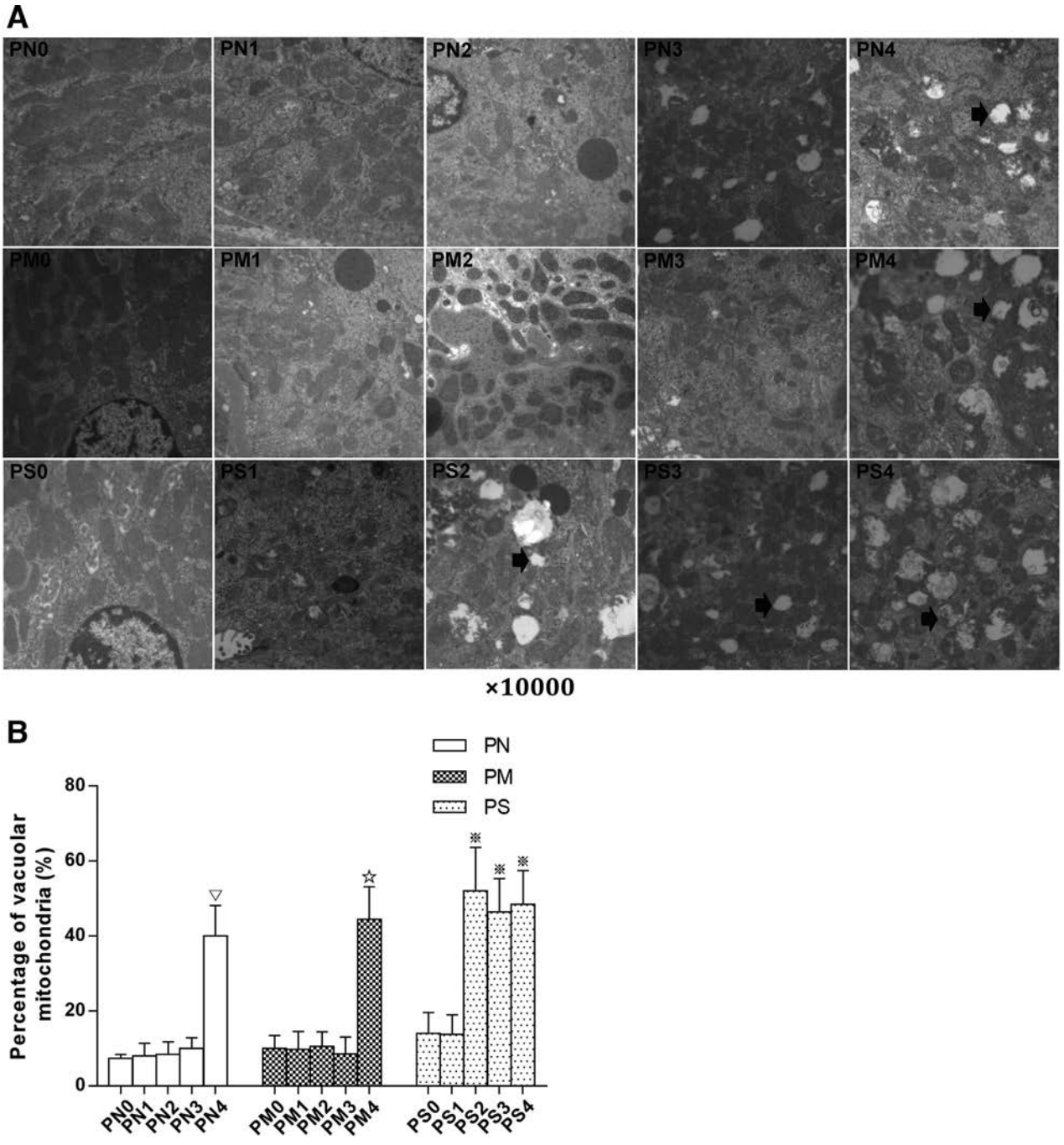

Figure 2. The ultrastructural changes of the mitochondria. (**A**) Swollen and vacuolar mitochondria in rabbits with mild and severe hydronephrosis under different perfusion pressures (×10000); the arrows show the swollen and vacuolar mitochondria. (**B**) The percentage of swollen and vacuolar mitochondria.PN0, PN1, PN2, PN3, and PN4 represent normal rabbits that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. PM0, PM1, PM2, PM3, and PM4 represent rabbits with mild hydronephrosis that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. PS0, PS1, PS2, PS3, and PS4 represent rabbits with severe hydronephrosis that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. $^{\triangledown}P$ <.05 compared with the PN0 group. $^{\star}P$ <.05, compared with the PM0 group. $^{\divideontimes}P$ <.05, compared with the PS0 group.

the MMP of renal tissues decreased significantly when the intra-abdominal pressure was elevated to 15 mmHg. However, in the severe hydronephrosis group, the MMP decreased significantly when the intra-abdominal pressure was elevated to only 9 mmHg. This difference could be explained by the different hydronephrosis treatment used, which resulted in different degrees of fibrosis. Because fibrosis is closely related to renal dysfunction,[17] more fibrotic kidneys were more vulnerable and had a weaker ability to protect against damage. The decrease in renal

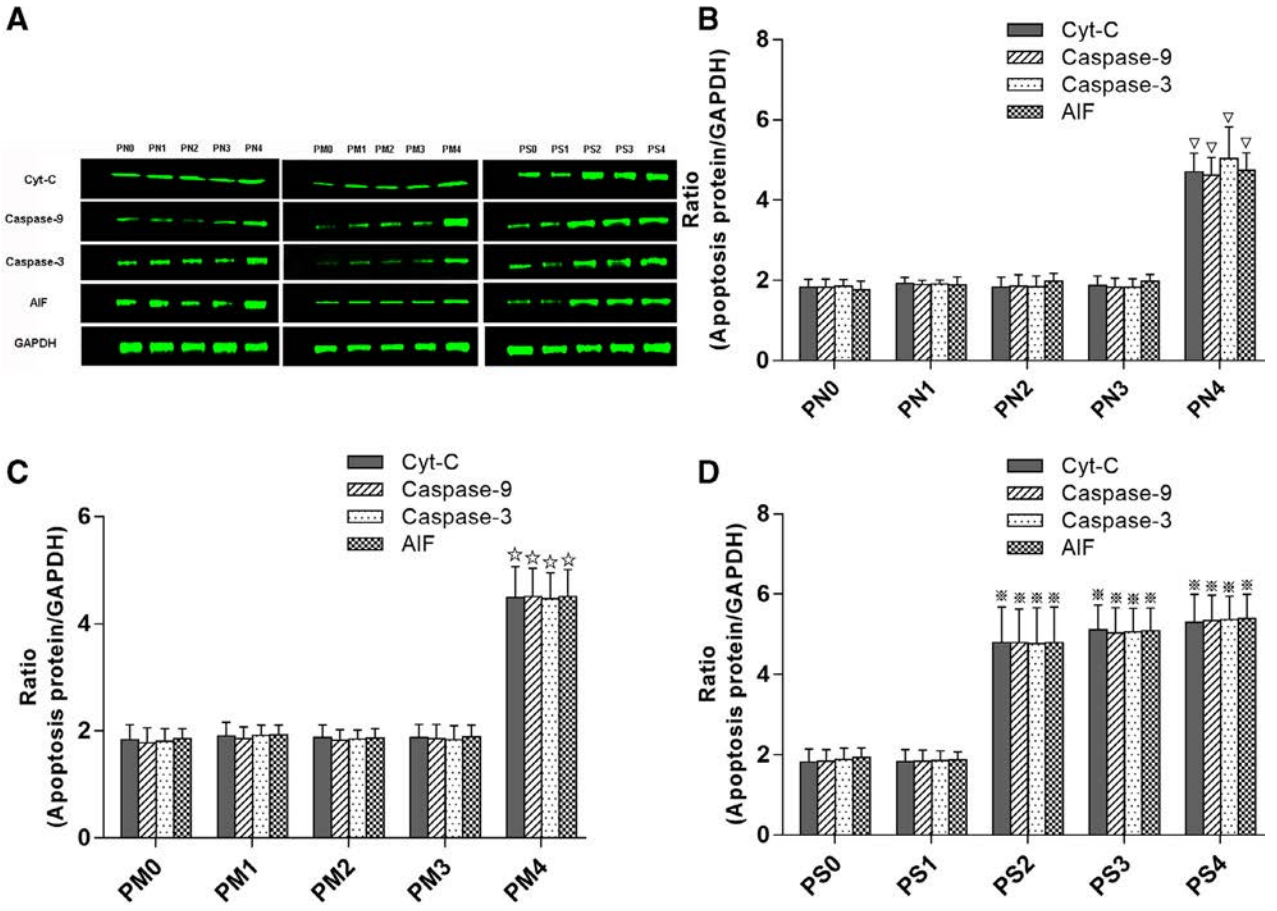

Figure 3. Expression levels of apoptosis proteins. (**A**) The expression levels of Cyt-C, caspase-9, caspase-3, AIF, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as shown by western blot analysis. (**B**) The statistical analysis of apoptosis protein expression level compared with GAPDH in all groups.PN0, PN1, PN2, PN3, and PN4 represent normal rabbits that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. PM0, PM1, PM2, PM3, and PM4 represent rabbits with mild hydronephrosis that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. PS0, PS1, PS2, PS3, and PS4 represent rabbits with severe hydronephrosis that were subjected to pneumoperitoneal pressures of 0 mmHg, 6 mmHg, 9 mmHg, 12 mmHg, and 15 mmHg, respectively. $^{\triangledown}P$ <.05, compared with the PN0 group. $^{\star}P$ <.05, compared with the PM0 group. $^{\ast\ast}P$ <.05, compared with the PS0 group. AIF, apoptosis-inducing factor.

MMP was more likely in more obstructed kidneys when encountering pneumoperitoneum pressure. The mild hydronephrosis kidneys were less fibrotic and had enough normal renal tissue to sustain normal MMP. This resulted in the mild hydronephrosis group displaying the same tolerance to pneumoperitoneum pressure as the normal group.

The mitochondria are the center of energy production. Mitochondrial injures not only cut-off the supply of energy on which oxidative respiration relies but also lead to the release of Cyt-C.[18] Hypoxia and ischemia can easily result from MMP disruption because considerable damage to the inner mitochondrial membrane leads to mitochondrial swelling and disruption of the cristae structures.[19,20] The loss of MMP and damage to mitochondria trigger the release of 2 crucial proapoptotic proteins, Cyt-C and AIF, from the mitochondria into the cytosol, leading to the induction of caspase activity in the cytosol and subsequently the apoptotic cascade.[21,22] Cyt-C binds to Apaf-1 and pro-caspase-9, which results in the auto cleavage of caspase-9 and activation of downstream caspases.[23] Finally, following the activation of caspase-3, which is responsible for the characteristic morphological changes of apoptosis, cellular apoptosis occurs.[24] AIF translocated into the cell nucleus where it binds with DNA, inducing chromatin condensation and DNA fragmentation.[25,26] In this study, we found that in the normal and mild hydronephrosis groups, swollen and vacuolar mitochondria significantly increased when the pneumoperitoneum pressure was elevated to 15 mmHg, and the expression levels of Cyt-C, AIF, caspase-3, and caspase-9 significantly increased at 15 mmHg. In the severe hydronephrosis group, the increase in swollen and vacuolar mitochondria and expression levels of Cyt-C, AIF, caspase-3, and caspase-9 occurred at 9 mmHg. These observations were in accordance with our previous study. In normal rat kidneys, it has been reported[3] that a 12 mmHg pneumoperitoneal pressure caused significant renal

apoptosis. Other reports showed that 8 mmHg of pneumoperitoneum was safe in the pig model.[27] All of the above studies were based on normal kidney experiments and used different animals as the experimentation model.

Additional studies using other animals should be carried out in the future. The pressure value which caused damage may be different in variant animal model. The surgical position effect on pneumoperitoneum pressure should also be considered in future studies.

The results of our animal study suggested that it may be beneficial for patients to control the intra-abdominal pressure during laproscopic surgery, especially in heavily hydronephrosis kidneys. Lower pneumoperitoneal pressure could improve the ability of hydronephrosis kidneys to resist mitochondrial injury.

CONCLUSION

The MMP level, ratio of mitochondrial vacuolization, and expression levels of the apoptosis proteins of severe hydronephrosis changed dramatically compared with mild ones when they were exposed to pneumoperitoneal pressure. Mitochondria were more easily suffered from damage in severe hydronephrosis than that in mild ones in the context of increasing with pneumoperitoneal pressure. Mitochondrial damage dependency plays an important role in the process of acute kidney injuries induced by intra-abdominal pressure.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.02.006.

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