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Alhusseinawi, Hayder

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BY
HAYDER ALHUSSEINAWI

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AALBORG UNIVERSITY
DENMARK

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by

Hayder Alhusseinawi

AALBORG UNIVERSITY
DENMARK

Dissertation submitted.

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PhD supervisor::	Prof. Sten Rasmussen Aalborg University
Assistant PhD supervisor:	Prof. Jørgen B. Jensen Århus University
	Associat. Prof. Pernille S. Kingo
PhD committee:	Clinical Professor Benedict Kjærgaard (chair) Aalborg University, Denmark
	Professor Christian Beisland University of Bergen, Norge
	Professor Palle Jörn Sloth Osther University of Southern Denmark, Denmark
PhD Series:	Faculty of Medicine, Aalborg University
Department:	Department of Clinical Medicine

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CV

Hayder Alhusseinawi, MD, is a Registrar in Urology at Aalborg University Hospital, Denmark. Upon completing his medical degree at Al-Kindey Medical School in Bagdad, Iraq, in 2006, he committed nine years to the healthcare system in his home country. This period encompassed his specialization in Urology at Alkarama Teaching Hospital.

His journey led him to Denmark, where he initially took up the role of a junior doctor at Aalborg University Hospital. Subsequently, he transitioned into his current position as a Registrar in Urology. This transition between healthcare systems endowed him with a broad scope of professional experience.

Hayder is steadfast in his pursuit of knowledge, actively seeking opportunities for development. He has undertaken extensive training in a multitude of areas, including surgical techniques and biostatistics, to fine-tune his proficiency. His external placements at the Bristol Urological Institute in the UK and Dandryts Hospital, Karolinska Institute in Sweden, further enhance his international exposure.

Further demonstrating his commitment to the field of urology, Hayder actively contributes to the medical community by sharing his knowledge and research findings through scientific articles and presentations at professional gatherings.

ENGLISH SUMMARY

This doctoral research investigates the implications of low pneumoperitoneum (Pnp) pressure on patient outcomes and surgical conditions during robot-assisted radical prostatectomy (RARP), with a specific focus on postoperative quality of recovery (QoR), renal function, surgical workspace, and feasibility of the procedure.

The first aspect of this research explored the effects of low Pnp pressure on postoperative QoR and surgical workspace in patients undergoing RARP for prostate cancer. A randomized, triple-blinded trial was conducted involving 98 patients assigned to either low Pnp pressure (7 mmHg) or standard Pnp pressure (12 mmHg). Findings highlighted that RARP performed at low Pnp pressure did not compromise the surgical workspace and significantly improved patient QoR on the first postoperative day. Notably, patients experienced significant improvements in pain, physical comfort, and emotional state domains. However, a minor increase in blood loss was observed in the low Pnp group.

Complementarily, the research evaluated the impact of low Pnp pressure on renal function during RARP. This arm of the study revealed that low Pnp pressure resulted in significantly lower levels of urinary neutrophil gelatinase-associated lipocalin (u-NGAL), a key marker of renal injury. Additionally, significant differences were observed in intraoperative and total postoperative urine production. Despite these findings, no significant difference in acute kidney injury (AKI) rates, as per the Kidney Disease Improving Global Outcomes (KDIGO) criteria, were observed between the low and standard Pnp groups.

Collectively, the research provides a nuanced understanding of the impacts of low Pnp pressure during RARP. The results suggest that low Pnp pressure enhances postoperative recovery and may reduce renal injury, even though a corresponding decrease in AKI rates wasn't observed. Moreover, it was found to be feasible without compromising the surgical workspace. These findings lay the groundwork for further research to validate the potential benefits of low Pnp pressure during RARP, aiming to optimize surgical strategies and ultimately improve patient outcomes. This doctoral work contributes to the body of knowledge on surgical conditions and patient recovery, offering new insights that can extend to other surgical procedures beyond prostatectomy.

DANSK RESUME

Denne doktorgradsforskning undersøger implikationerne af lavt pneumoperitoneum (Pnp) tryk på patient reporteret resultater og kirurgiske forhold under robotassisteret radikal prostatektomi (RARP), med særligt fokus på postoperativ kvalitet af rekonvalescens, nyrefunktion, kirurgisk arbejdsforhold, og procedurens gennemførlighed.

Det første aspekt af denne forskning udforskede effekterne af lavt Pnp tryk på postoperativ rekonvalescens og det kirurgiske arbejdsforhold hos patienter, der gennemgik RARP for prostatakræft. En randomiseret, triple-blindet forsøg blev udført med 98 patienter, der blev tildelt enten lavt Pnp tryk (7 mmHg) eller standard Pnp tryk (12 mmHg). Resultaterne viste, at RARP udført ved lavt Pnp tryk ikke kompromitterede det kirurgiske arbejdsforhold og signifikant forbedrede patientens rekonvalescens på den første postoperative dag. Specifikt oplevede patienterne signifikante forbedringer i smerte, fysisk komfort og følelsesmæssige tilstand. Dog blev et øget blodtab observeret i den lave Pnp gruppe.

Komplementært evaluerede forskningen effekten af lavt Pnp tryk på nyrefunktionen under RARP. Denne del af studiet viste, at lavt Pnp tryk resulterede i signifikant lavere niveauer af urin-neutrofil gelatinase-associeret lipocalin (u-NGAL), en nøglemarkør for nyreskade. Desuden blev der observeret signifikante forskelle i intraoperativ og total postoperativ urinproduktion. På trods af disse resultater var der ingen signifikant forskel i akut nyreskade (AKI) rater mellem den lave og standard Pnp grupper.

Samlet set giver forskningen en nuanceret forståelse af virkningerne af lavt Pnp tryk under RARP. Resultaterne antyder, at lavt Pnp tryk forbedrer postoperativ rekonvalescens og kan muligvis reducere nyreskade, selvom et tilsvarende fald i AKI rater ikke blev observeret. Desuden blev det fundet at være gennemførligt uden at kompromittere det kirurgisk arbejdsforhold. Disse resultater lægger grundlaget for yderligere forskning for at validere de potentielle fordele ved lavt Pnp tryk under RARP, med det formål at optimere kirurgiske strategier.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude to my supervisor, Professor Sten Rasmussen, M.D., Ph.D. His continuous support, invaluable guidance, and steadfast belief in my capabilities were instrumental in my journey into the field of science and academic writing. His mentorship has been a beacon that consistently illuminated my path throughout this journey.

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This Ph.D. dissertation is the culmination of my enrollment as a Ph.D. student at the Department of Clinical Medicine, Aalborg University, from 2020-2023. I want to extend my heartfelt appreciation to the institution and its faculty for fostering an environment conducive to learning and for their unending faith in my abilities.

A special note of thanks goes to my Department of Urology and particularly to the head of the department, Doctor Thomas Halphen, whose relentless support was crucial for the completion of this thesis. I am also indebted to all my colleagues and nurses in the department whose camaraderie, team spirit, and consistent dedication to the profession were a continuous source of motivation.

Finally, none of this would have been possible without the love, patience, and unyielding support of my family. I would like to express my deepest gratitude to my wife for her ceaseless encouragement and patience during this journey. Her strength in managing our home and caring for our four children single-handedly in my absence is a testament to her resilience and love.

To my children, Maryam, Mustafa, Mina, and Dania, thank you for your understanding, smiles, and endless enthusiasm, which have brought much-needed balance and joy into my life during this challenging journey.

This journey has been a team effort, and this dissertation stands as a testament to the collective hard work, dedication, and faith of everyone involved. Thank you.

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LIST OF ABBREVIATIONS

Pnp - Pneumoperitoneum

PCa - Prostate Cancer

RARP - Robot-Assisted Radical Prostatectomy

CO – Cardiac Output.

MAP - Mean Arterial Pressure.

SVR - Systemic Vascular Resistance

POI – Post-Operative Ileus

GFR – Glomerular Filtration Rate

RAAS- Renin-Aldestrone-Angiotensin- System

QoR - Quality of Recovery

POD - Postoperative Day

SWS - Surgical Workspace Scale

ODP - Operating Department Practitioner

ITT- Intention to treat

AKI - Acute Kidney Injury

KDIGO - Kidney Disease Improving Global Outcomes

SCr - Serum Creatinine

ELISA - Enzyme-Linked Immunosorbent Assay

u-NGAL - Urinary Neutrophil Gelatinase-Associated Lipocalin

KIM-1 - Kidney Injury Molecule-1

VEGF - Vascular Endothelial Growth Factor

u-ACR - Urinary Albumin-Creatinine Ratio

CI - Confidence Interval

IQR - Interquartile Range

CV - Coefficient of Variation

OA - Osteoactivin (also known as gpnmb - Glycoprotein Non-Melanoma Clone B)

MOE – Morphine Oral equivalent

NMB – Neuromuscular blockade

CHAPTER 1. INTRODUCTION

In 1910, Hans Christian Jacobson (1879–1937), a Swedish internist, conducted the first diagnostic laparoscopic procedure. Pioneering a novel approach, he introduced a functional space between the abdominal wall and the internal organs by inserting a trocar and inflating it with filtered air. Upon achieving adequate inflation for visualisation, Jacobson repurposed a cystoscope, typically used for bladder inspection, as a telescope for abdominal exploration[1]. This laparoscopic technique inspired surgeons globally, marking the genesis of minimally invasive surgery, specifically laparoscopic surgery.

Over time, various insufflation gases have been examined. The optimal insufflant remains unidentified, but in its absence, carbon dioxide (CO2) has proven to be the most suitable substitute due to its minimal complications and discomfort[2].

Compared with traditional open surgery, minimally invasive surgery offers several benefits, including avoiding large incisions, which leads to reduced blood loss, pain, discomfort, and shorter hospital stays. Patients experience fewer side effects from analgesics, as less analgesia is needed[3–5].

1.1. ELEVATED INTRAABDOMINAL PRESSURE

Notwithstanding its advantages, initiating pneumoperitoneum in surgery, through the insufflation of CO2 into the peritoneal cavity, triggers a sequence of physiological alterations in several organs[6]. These physiological changes are influenced by increase in Intraabdominal Pressure (IAP) and hypercapnia resulting from CO2 absorption (Figure 1.1). It is understood that an increased pneumoperitoneum (Pnp) up to 12-15 mmHg, diminishes venous return, thereby resulting in a decrease in preload and cardiac output in the absence of adequate intravascular volume loading[7]. The high Pnp lead to increased airway pressures, and decreased pulmonary compliance Moreover, CO2 is rapidly absorbed, leading to hypercapnia and resultant respiratory acidosis[8].

Furthermore, direct compression of the abdominal aorta, coupled with a neuroendocrine response marked by increases in plasma norepinephrine, epinephrine, cortisol, and vasopressin, leads to an elevation in mean arterial pressure (MAP) and systemic vascular resistance (SVR)[9].

These vascular changes result in diminished blood flow to splanchnic organs. An increase in liver enzymes is observed as a response to a decrease in hepatic arterial and portal venous blood flow [10], while a reduction in mesenteric blood flow may

delay postoperative bowel function and heighten the risk of postoperative ileus (POI)[11].

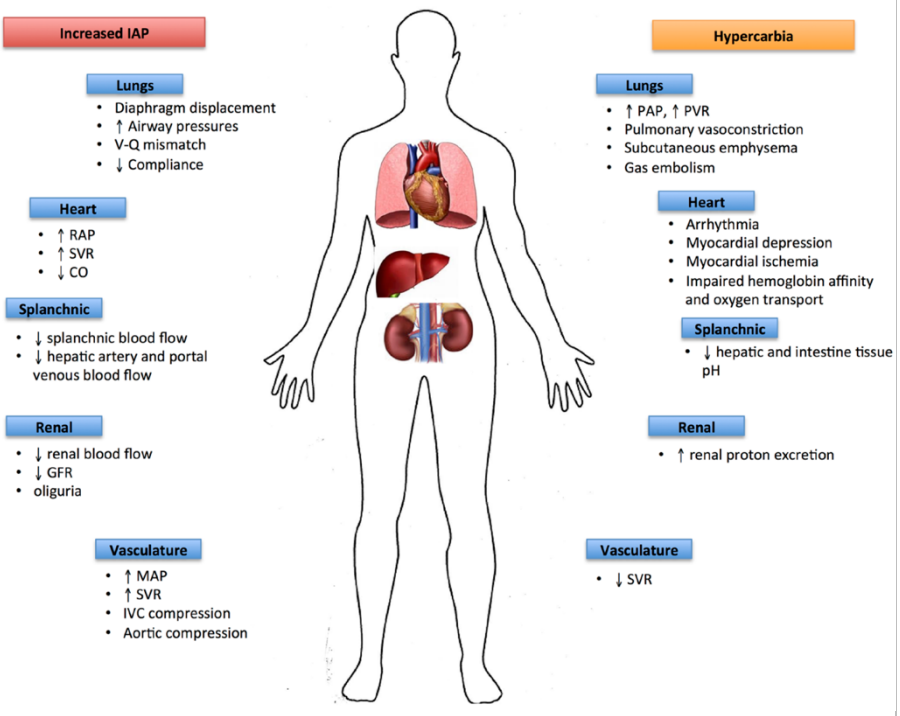

Figure 1.1 Two components of laparoscopic surgery.

Detrimental effects of increased IAP and hypercarbia are listed. CO indicated cardiac output; GFR, glomerular filteration rate; IAP, intraabdominal pressure; MAP, mean arterial pressure; PAP, pulmonary artery pressure; RAP, right atrial pressure; and SVR, systemic vascular resistance. Reproduced with permission from Dr. Joaquin E. Cigarroa, Cardiovascular and Ventilatory Consequences of Laparoscopic Surgery, *Circulation* 2017; 135: 700–710

1.2. CHANGES IN KIDNEY PHYSIOLOGY AND RISK OF ACUTE KIDNEY INJURY (AKI)

Elevated intra-abdominal pressure (Pnp) is associated with complex renal changes. However, the precise mechanism behind this has not been fully elucidated[12]. Based on both animal and human studies, it is postulated that these alterations are likely attributable to a combination of direct, indirect, and neurohormonal effects. Direct effects might encompass Pnp-induced compression of the renal parenchyma, vasculature, renal pelvis, and ureter, potentially culminating in diminished renal blood flow, a decrease in the glomerular filtration rate (GFR), and oliguria[13]. Indirect effects are linked to the Renin-Angiotensin-Aldosterone system (RAAS) activation, CO2 absorption, and cellular disruption prompted by oxidative stress[9, 14–17]. Neurohormonal changes, characterised by an increase in plasma Antidiuretic hormone (ADH) following the insufflation of CO2 into the peritoneal cavity, are also noteworthy. Research has highlighted a significant elevation in ADH levels during laparoscopic surgery compared to open procedures, resulting in water and sodium retention[18].

In healthy individuals, particularly the young or those without pre-existing renal disease, these physiological alterations triggered by elevated Pnp can frequently be compensated for via various intrinsic mechanisms. The kidneys inherently possess the capacity to maintain a relatively constant renal blood flow and GFR in spite of systemic changes, an attribute referred to as renal autoregulation. Additionally, the activation of RAAS and ADH enhances sodium and water reabsorption to maintain blood volume and systemic blood pressure[19]. Furthermore, tubuloglomerular feedback contributes to the preservation of renal function by adjusting the GFR in response to changes in sodium chloride concentration at the distal tubule[20]. Preclinical studies have suggested that these compensatory mechanisms may be overwhelmed in the face of high Pnp or prolonged duration of surgery, potentially leading to acute kidney injury (AKI)[21].

According to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI is defined as an increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours, or an increase in SCr to 1.5 times baseline, known or presumed to have occurred within the prior seven days, or urine volume ≤0.5 ml/kg/h for 6 hours.[22]

While SCr is the principal determinant in the KDIGO definition of AKI, it is not an ideal marker of renal function. Firstly, a substantial delay can occur between the onset of kidney injury and a rise in serum creatinine levels. This is because the kidneys possess a large functional reserve, and a significant reduction in kidney

function can transpire before creatinine levels elevate.[23] Secondly, creatinine, a byproduct of muscle metabolism, can be influenced by factors such as muscle mass, diet, and certain medications, potentially leading to false positive or false negative results.[24]

In recent years, numerous urinary biomarkers have been identified as indicators of renal damage. These markers represent promising alternatives to creatinine, as they can detect AKI early and are expressed in specific nephron segments. [25–31] Figure 1.2 lists these biomarkers and their respective expression sites in the nephron. Changes in the levels of these biomarkers during laparoscopic or robot-assisted procedures could provide invaluable insight into the renal physiological alterations induced by elevated Pnp. Monitoring these markers can contribute to the early identification of individuals at risk for developing AKI, thereby allowing for timely intervention and potentially improving patient outcomes.

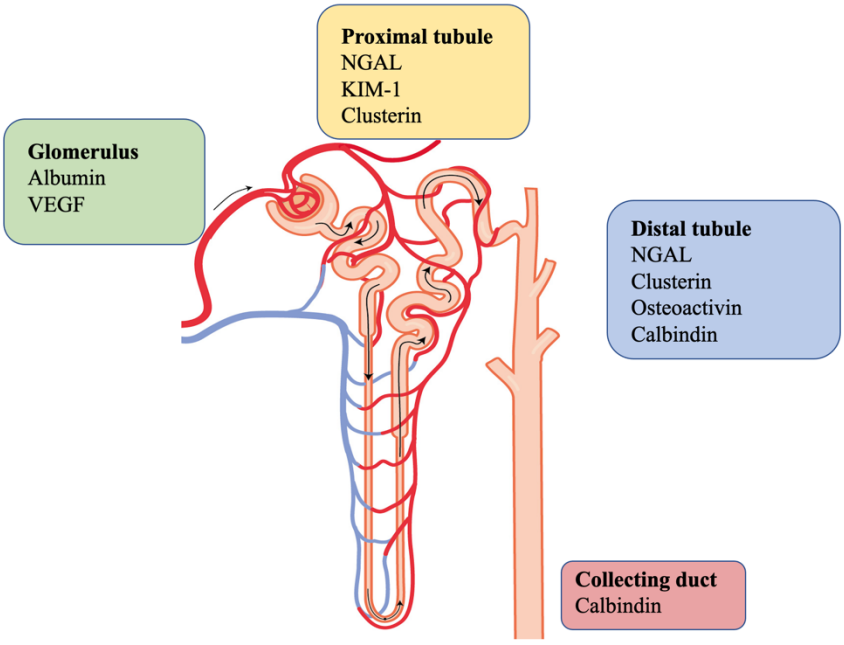

Figure 1.2 Biomarkers of Acute Kidney Injury (AKI) and Their Sites of Expression within the Nephron. This diagram illustrates various biomarkers associated with AKI and their corresponding locations within the nephron, providing a clearer understanding of where these biomarkers originate. AKI: Acute Kidney Injury, VEGF: Vascular Endothelial Growth Factor, NGAL: Neutrophil Gelatinase-Associated Lipocalin, KIM-1: Kidney Injury Molecule-1. [25–31]

1.3. SURGICAL WORSKSPACE

Currently, a multitude of surgical procedures are conducted with a Pnp of 12-15 mmHg [32], despite international guidelines advocating for use of ”the lowest Pnp possible allowing adequate exposure of the operative field rather than using a routine pressure level”.[12] The application of low insufflation pressure could mitigate some of the negative impacts of pneumoperitoneum on cardiac, pulmonary, and renal physiology and reduce pain.[12] However, the safety and feasibility of performing surgery using laparoscopy or robot-assisted laparoscopy at low Pnp necessitate an evaluation of the surgical field to guarantee the possibility of operation completion with minimal complications, and without restricting the surgeon's view or access to instruments during the procedure.

During laparoscopic or robotic-assisted laparoscopic surgery, a surgeon may implement several measures to optimise intra-abdominal visibility and the ease of instrument manoeuvring. These can include instructing the anesthesiologist to administer more muscle relaxants, evaluating the potential for gas leakage, arranging for smoke evacuation, or increasing Pnp.

The assessment of the surgical workspace during laparoscopic procedures has typically relied on various subjective rating scales utilised in different studies. As underscored by a scoping review by Boon et al., inconsistencies and deficiencies in the quality and methodologies of surgical rating scales of the workspace persist, with many scales being poorly described and lacking assessments of inter- and intra-rater reliability. [33] Two rating scales were previously validated in the literature. The evaluation of workspace has become more nuanced with the advent of the (Lieden-Surgical rating scale (L-SRS), a surgical rating scale employed in a study on during laparoscopic surgery in patients with moderate vs deep neuromuscular block. This scale, designed by anesthetists, ranks workspace on a 1-5 Likert scale, with muscle relaxation being the only potential intervention considered to enhance workspace.[34]

An important refinement to the L-SRS was made by Nervil et al., who added the increase of Pnp as another plausible intervention to improve the workspace. Yet, minor interventions suggested by their scale, like changes in patient or surgeon position, don't transfer well to the context of robotic surgery. This precipitated the necessity for adapting and revalidating the scale for application in robotic surgery, which also required confirmation of its inter and intra-rater reliability.

1.4. QUALITY OF POSTOPERATIVE RECOVERY

The rapid restoration of pre-operative cognitive and physical function following radical operations is critical for cancer patients, considering both their quality of life and the wider implications for health economics.

Surgeons and anaesthesiologists have developed numerous questionnaires to assess the rate at which patients regain their pre-operative physical and mental status. The Quality Recovery-15 (QoR-15), a recognised and validated questionnaire used extensively in Denmark and many other countries, is one such tool.[35, 36] This questionnaire consists of 15 items, each rated on a scale from 1 to 10, that evaluate physical well-being (including aspects such as pain, physical comfort, and physical independence) and mental well-being (encompassing psychological support and emotional state). (See Appendix D,E)

In recent years, several studies have sought to determine the importance of reducing Pnp during laparoscopic/robot-assisted laparoscopic procedures such as cholecystectomy, colo-rectal surgery, hysterectomy, and prostatectomy.[37–42] Investigations into the feasibility and benefits of low Pnp surgery, particularly in the context of radical prostatectomy, have primarily focused on the post-operative use of analgesia, risk of bleeding, operation time, duration of admission, and post-operative ileus. To date, no published randomised trials have studied the impact of low-pressure pneumoperitoneum on postoperative quality of recovery (QoR). Similarly, the effect of low pneumoperitoneum on acute kidney injury urinary biomarkers remains unexplored. Furthermore, studies assessing the surgical workspace during low Pnp Robot-Assisted Radical Prostatectomy (RARP) utilising the aforementioned SWS are scant.

Therefore, our research question arises: How does low-pressure pneumoperitoneum during RARP affect the quality of postoperative recovery, as measured by the Quality Recovery-15 (QoR-15) questionnaire, the incidence of acute kidney injury urinary biomarkers, and the assessment of surgical workspace via the Surgical Workspace Score (SWS)?

CHAPTER 2. AIMS AND HYPOTHESIS

Aim:

The primary aim of this thesis was to investigate the potential advantages and drawbacks of implementing low Pneumoperitoneum (Pnp) pressure during Robot-Assisted Radical Prostatectomy (RARP) compared to the standard Pnp. The study focused on three key parameters: the postoperative quality of recovery, the risk of Acute Kidney Injury (AKI), and the implications for the surgical workspace (including validation of the surgical workspace scale (SWS))

The study was designed as a randomised clinical trial, with patients assigned to either an intervention group (RARP under low Pnp) or a control group (RARP under standard Pnp). Data were collected throughout the perioperative period, with particular emphasis on clinical and functional outcomes, alterations in AKI biomarkers, and assessments of the surgical workspace.

Hypotheses and Specific Aims:

Hypothesis I:

Employing low Pnp during RARP will enhance the postoperative quality of recovery, as indicated by patient-reported questionnaires.

Aim I:

To assess the impact of low Pnp during RARP on the postoperative quality of recovery using patient-reported questionnaires.

Hypothesis II:

Low Pnp during RARP could compromise the surgical workspace, thereby increasing the risk of organ injury and bleeding.

Aim II:

To evaluate the effect of low Pnp on the surgical workspace during RARP.

Hypothesis III:

The use of low Pnp during RARP may decrease the incidence of AKI, as assessed by urinary Neutrophil Gelatinase-Associated Lipocalin (u-NGAL) and other AKI biomarkers.

Aim III:

To investigate the potential of low Pnp during RARP to reduce the incidence of AKI, as evidenced by u-NGAL.

CHAPTER 3. METHODOLOGICAL CONSIDERATION

3.1. STUDY DESIGN AND PARTICIPANTS

This is a single-centre, triple-blinded randomised clinical trial conducted at the Department of Urology, Aalborg University Hospital, Aalborg, Denmark. We included patients aged between 40 and 75 with previously untreated, histologically confirmed, focal prostate cancer who were offered robot-assisted radical prostatectomy (RARP). Exclusion criteria were the inability to give informed consent, complete trial documentation, or communicate in the Danish language. This study is in compliance with the Declaration of Helsinki. It has been approved by the Ethics Committee of the North Denmark Region (N-20200078, 08. December 2020) and the Danish Data Protection Agency (2020-118, 28. September 2020). It was registered at ClinicalTrials.gov (NCT04755452, 16. February 2021). All patients provided written informed consent, and the trial proceeded according to Good Clinical Practice and CONSORT guidelines.[43] Participants were randomly assigned in a 1:1 ratio to either a low Pnp group (7 mmHg) or a standard Pnp group (12 mmHg).

3.2. PROCEDURE

All surgical procedures were performed by two experienced surgeons, each having completed more than 300 RARPs prior to the commencement of the study. Surgeries were conducted in the steep Trendelenburg position in accordance with the method outlined by Huynh et al.[44] Following the administration of general anaesthesia, a urinary catheter was inserted by the operating department practitioner (ODP). The ODP collected a 20 mL urine sample and recorded intraoperative urine production. During the operation, the Surgical Workspace Score (SWS) was utilised by the surgeons to evaluate the surgical workspace. Scores from 1 to 5 were assigned at three different stages: 1) at the incision of the bladder neck, 2) during the dissection of the seminal vesicle, and 3) during the dissection of the prostate's apex. In all cases, the dorsal venous complex (DVC) was controlled using a suture ligation technique, and the Pnp pressure remained consistent during the DVC dissection to maintain procedure uniformity. Postoperative care was standard for all patients, including early mobilisation, clear fluid intake, pain management, and administration of prophylactic anticoagulants. Discharge typically occurred the day following surgery, once patients were comfortable.

On the day of discharge, a second 20 mL urine sample was taken immediately prior to the patient leaving the ward. These samples were preserved at -80°C for future analysis of urinary markers of kidney injury. Blood tests for serum creatinine were performed one week prior to surgery, on the first day post-surgery, and again on the tenth-day post-surgery. To track recovery progress, co-researchers reached out to patients before the surgery, and on postoperative days (POD) 1, 3, 14, and 30 to complete the QoR-15 questionnaire.

3.3. RANDOMISATION ANS MASKING

Data collection and online randomisation were carried out using the RedCap (Research Electronic Data Capture) software, managed by Aalborg University Hospital. The distribution of patients was balanced, with a 1:1 ratio between a low Pnp group (7 mmHg) and a standard Pnp group (12 mmHg). The primary investigator organised the randomisation process, finalising it when the patient was in the operating theatre. After the patient was anaesthetised, a sealed envelope that contained the group allocation was given to the ODP in the operating room. Patients were unaware of the group to which they were allocated. The surgeon was instructed to adjust all surgical ports at Pnp = 10–12 mmHg. Once port placement and robot docking were completed, the ODP opened the envelope and adjusted the Pnp as per the designated pressure group. To maintain blinding, the nurse covered the pressure indicator on the insufflator, ensuring that the surgeon was unaware of the pressure group assignment. In addition, the two co-researchers responsible for conducting the patient questionnaire were kept uninformed of the randomisation status of the patients.

3.4. OUTCOMES

In the first study, the primary outcome was the variation in the QoR-15 score. Secondary outcomes included an analysis of QoR-15 domains (pain, physical comfort, physical independence, psychological support, and emotional state), , length of hospital stay, complications within 90 days post-operation (utilising the Clavien-Dindo classification),[45] and opioid use in the first 24 hours as measured by morphine oral equivalent (MOE).[46]

The second study's primary outcome was the change in the SWS, which was assessed three times intraoperatively. The secondary outcome were blood loss during the procedure, and operation time.

For the third study, the primary outcome focused on the changes in urinary Neutrophil Gelatinase-Associated Lipocalin (u-NGAL) before and after surgery. Secondary outcomes involved changes in various urinary markers, electrolytes, intraoperative urine production, and the risk of AKI as per the KDIGO criteria.

3.4.1. BIOCHEMICAL ANALYSIS

The biochemical analysis of u-NGAL, other urinary biomarkers, and electrolytes were conducted at the Department of Clinical Biochemistry, Aalborg University Hospital. The detailed techniques and procedures for this analysis are thoroughly described in the methods section of our third article (Appendix C)

3.5. SAMPLE SIZE

The sample size was calculated based on the minimum clinically important difference (MCID) for the primary outcomes of both the first and the second studies, namely the QoR-15 and the SWS. The MCID is a metric used to signify the smallest change in a treatment outcome that is meaningful for the patient.[47] This parameter plays a critical role in power and sample size calculations as it reflects a significant difference from the patient's perspective. The suggested minimal clinically important difference (MCID) for the QoR-15 was 10 points with a standard deviation of 16, and for the SWS, it was 0.5 with a standard deviation of 0.4. These MCIDs were grounded on a comprehensive review of relevant literature and consultations with specialists.[35, 48, 49]

Power analysis, used to calculate the required sample size, is a statistical method for determining the likelihood of detecting a true effect if one exists. In this context, the "power" (1-β) is the probability of avoiding a Type II error, which occurs when a study incorrectly fails to reject a false null hypothesis (i.e., erroneously concludes that the intervention has no effect). In contrast, a Type I error (α) occurs when a study wrongly rejects a true null hypothesis (i.e., mistakenly infers that the intervention has an effect when it does not). Both types of errors can lead to incorrect conclusions about the efficacy of an intervention, which underscores the importance of power analysis in study design.

To detect the differences in MCID with sufficient power, we determined that 84 patients (42 in each group) were needed. This would provide an 80% power (1-β) to show a difference in QoR-15 and over 98% power to detect a difference in the SWS at a two-sided alpha (α) of 0.05, meaning a 5% chance of falsely claiming a significant effect (Type I error).

Considering a potential loss to follow-up of about 15%, we aimed to recruit a total of 100 patients to ensure adequate power for our analyses. All analyses were conducted based on the intention-to-treat population. The intention-to-treat principle ensures that all randomised participants are included in the analysis, which prevents bias that could arise from excluding participants based on post-randomization events.

Regarding the third study, a separate sample size calculation was not conducted specifically for this part of the research. Our sample size of 100 patients from the first study was already sufficient, as it was larger than the required sample size needed to detect differences in u-NGAL levels based on previous studies. [50–52]This provided us with ample power to conduct meaningful analyses for the third study.

The sample size was calculated using this formula.

$n = [(Z_{\alpha/2} + Z_{\beta})^2 * 2\sigma^2] / (\mu1 - \mu2)^2$

Where:

n: The required sample size for each group.

$Z_{\alpha/2}$: The critical value of the Normal distribution at $\alpha/2$ (for a confidence level of 95%, this is 1.96).

Z_{β}: The critical value of the Normal distribution at β (for a power of 80%, this is approximately 0.84).

σ: is the standard deviation of the groups.

$\mu1 - \mu2$: The difference in means between the two groups.

3.6. STATISTICS

Statistical analysis was performed using STATA (version 17). All analyses were based on the intention-to-treat (ITT) population. For continuous data, the mean, standard deviation, and 95% confidence interval, or median and interquartile range

(IQR), were reported for non-parametric data. Categorical data were presented as numbers.

A repeated measures model using a robust variance estimate was used not only to estimate mean differences and 95% confidence intervals for the total score of the QoR-15 but also to calculate changes in u-NGAL and other urinary biomarkers. This analysis technique allowed us to account for the correlated nature of repeated measurements on the same subjects, providing a more accurate estimate of the treatment effects over time.[53]

The Chi-square test was employed to evaluate between-group differences for categorical variables. Continuous variables were analysed using the t-test or nonparametric Mann-Whitney U test, depending on the data distribution. No imputation of missing data was performed, maintaining the integrity and validity of our data set.

The statistical analyses were designed to support the study's primary and secondary objectives, ensuring that our results provided clear, meaningful insights to answer our research questions. Significance was set at a two-sided alpha level of 5%.

3.7. VALIDATION OF SURGICAL WORKSPACE SCALE DURING ROBOTIC SURGERY

We refined a surgical workspace scale, drawing from previous surgical rating scales (SRSs) but tailoring it to robotic-assisted surgeries. It was built in collaboration with an experienced robotic surgeon and graded conditions as extremely poor, poor, acceptable, good, and optimal. Specific interventions, such as muscle relaxation adjustments, Pneumoperitoneum (PnP) status assessment, gas leakage checks, and guidance of bedside assistants, were included for each condition [Details in Appendix A validation study][54], Table 1.4

To validate this scale, we undertook a prospective cohort study at our centre. Patients aged over 18 who were diagnosed with renal tumours and underwent robot-assisted radical nephrectomy between February and April 2021 were enrolled. A total of 32 videos were systematically recorded from eight selected patients, capturing a range of workspace conditions by varying PnP pressure. These videos were then duplicated, randomised, and assessed by eight experienced robotic surgeons via an online survey using our surgical workspace scale.

Reliability was evaluated using inter-class and intra-class correlation coefficients (ICC) with a target of 0.8, indicating strong agreement. We also deployed a Fleiss-weighted (quadratic) kappa to assess inter-rater reliability. Our study aimed for ICC values above 0.75, denoting good to excellent reliability.

1. *Extremely poor conditions*: The surgeon is unable to work due to the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation or low intra-abdominal pressure. Additional muscle relaxants must be given, or intra-abdominal pressure should be increased
2. *Poor conditions*: There is a visible laparoscopic field, but the surgeon is severely hampered by small room with the hazard of tissue damage. Additional muscle relaxants must be given, or intra-abdominal pressure should be increased
3. *Acceptable conditions*: There is a wide visible laparoscopic field, but still some interference with the surgeon's work. After **one or two** minor adjustments surgery can be completed
4. *Good conditions*: There is a wide laparoscopic working field, but there is some interference, but no need for adjustments
5. *Optimal conditions*: The laparoscopic working field is optimal, and procedure can be completed without any interference

Minor intervention
1. Asses the possibility of gas leakage
2. Specific direct guidance of assistance
3. Assess relaxation status with anaesthetist

Table 3.1: Surgical Workspace Scale for Robotic Surgery

This table outlines the five levels of surgical workspace conditions in robotic surgery, along with potential interventions. It covers visibility and interference factors in the laparoscopic field and suggests steps for improvement under poor conditions, such as muscle relaxation and intra-abdominal pressure. Minor interventions like checking for gas leakage and assessing muscle relaxation status are also included.

3.8. LITERATURE (EVIDENCE BEFORE THIS STUDY)

The standard pneumoperitoneum (Pnp) pressure used during minimally invasive surgery (MIS) is routinely set at 12-15 mmHg. However, the choice to use this pressure level is based more on routine and habit rather than on evidence. According to the European Association of Endoscopic Surgery (EAES) guideline, it is recommended to use the lowest possible Pnp to decrease the physiological changes caused by rapidly expanding intraperitoneal space[12]. Many studies have investigated the advantages and feasibility of low Pnp during abdominal surgeries, but trials implementing low Pnp during urological procedures are scarce. We searched PubMed on September 22, 2022, with no date or language restriction using the terms ((((("low intra-abdominal pressure") OR ("ultra-low pneumoperitoneum")) OR ("low pneumoperitoneum")) OR ("Pneumoperitoneum"[Mesh] OR "Pneumoperitoneum, Artificial"[Mesh])) AND (("Prostatectomy"[Mesh]) OR ("prostatectomy")). We did not identify a clinical study investigating the impact of low Pnp on the quality of postoperative recovery, surgical workspace, or renal injury.

The cumulative analysis of a recently published meta-analysis (September 2022) found a reduced length of hospital stay and a reduced rate of postoperative ileus when lower Pnp was used. There was no significant increase in the length of operation, estimated blood loss, 30-day readmissions, or positive surgical margins. [55]The meta-analysis did not include two additional recent randomised clinical trials (RCTs), that we can identify in our UpToDate literature search.

The first trial investigated the risk of post-operative ileus as a primary outcome and did not find a significant difference between two groups of patients who underwent RARP at either standard (12 mmHg) or low (8 mmHg) Pnp.[11] The second trial examined the effect of standard Pnp on post-operative pain. They found that patients who had surgery at 6 mmHg had less post-operative pain.[56] The secondary outcomes from the two RCTs showed no significant difference in terms of postoperative ileus, length of hospital stay, estimated blood loss, positive surgical margin, or total operation time.

CHAPTER 4. SUMMARY OF RESULTS

4.1. RESULTS FROM THE VALIDATION STUDY

The results demonstrate moderate to excellent reliability in the surgical workspace scale for robotic surgery. For the inter-rater agreement between surgeons, an Intraclass Correlation Coefficient (ICC) of 0.74 [95% Confidence Interval (CI): 0.66-0.81] was observed, implying moderate reliability. The intra-rater reliability, essentially the test-retest reliability of eight surgeons, fell within the good to excellent reliability range. The ICC ranged between 0.80 (0.62–0.89) and 0.98 (0.97–0.99), with a pooled ICC of 0.89 (0.86–0.91) [See in Appendix A, Table 3,4 for details of intra-,inter-rater reliabilities of SWS]

While all surgeons used the full-scale range from 1 to 5 almost equally, item 3 was utilised more frequently, accounting for 30% of the usage.

4.2. RESULTS FROM A RANDOMISED STUDY

During the period from April 2nd, 2021, to January 28th, 2022, a total of 98 patients were included in our study. They were evenly divided into two groups: one group of 49 patients received the standard Pnp of 12 mmHg, and the other group of 49 patients were treated with a low Pnp of 7 mmHg.

4.2.1. THE EFFECT OF LOW PNP ON THE POSTOPERATIVE QUALITY OF RECOVERY

Figure 4.1 illustrates the flow of patients, and table 4.1 presents the characteristics of patient groups.

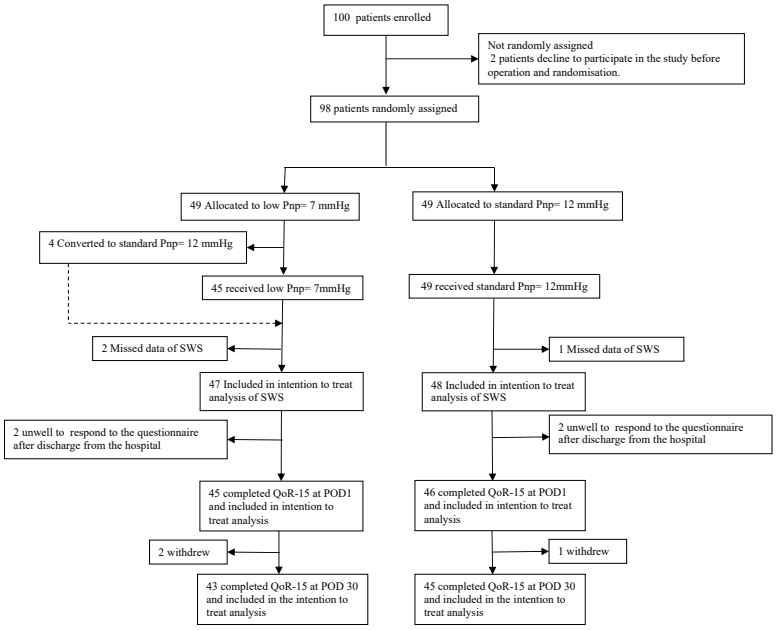

Figure 4.1 Patient Allocation and Follow-Up in QoR-15 (quality of Recovery-15) and SWS (Surgical workspace scale) Analysis: A CONSORT Flow Diagram

On the first postoperative day, the QoR-15 score was significantly higher in the low Pnp group (124.8 with 95% CI 120.8-128.9) compared to the standard Pnp group (114.8 with 95% CI 110.2-119.4), indicating better quality of recovery (Figure 4.2). The low Pnp group demonstrated a statistically significant improvement in the domains of pain, physical comfort, and emotional state compared to the standard Pnp group . [See Appendix B, Table 2 for details on the values of the domains of the post-operative QoR-15 questionnaire.]

	Standard Pnp (n=49)	**LowPnP (n=49)**
Age, year	66.9 (6.3)	65.5 (7.0)
BMI	27.1 (2.8)	28.0 (3.5)
Hypertension	19	22
DM	5	4
Previous abdominal surgery	5	6
PSA	11.1 (7.5)	10.3 (6.7)
Prostate volume, ml	54.3 (25.7)	51.8 (28.9)
T stage from DRE		
T1c	24	28
T2a	9	11
T2b	12	6
T2c	4	4
ISUP grade		
2	16	19
3	16	12
4	3	4
5	14	14

Data presented as mean (SD) for continuous variables, and as n (%) for categorical variables. There is no baseline missing data. PSA=prostate specific antigen.DRE= digital rectal examination. ISUP grade: International Society of Urologic Pathologists.

Table 4.1 : Baseline characteristics of the patients

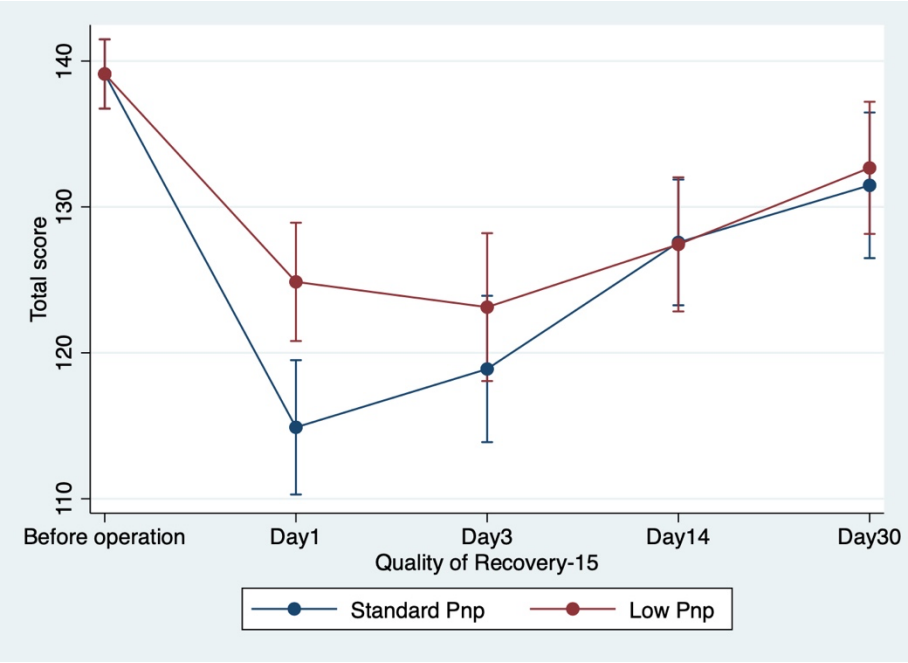

Figure 4.2 Results of total QoR-15 between low Pnp and Standard Pnp group. Data presented as mean and 95%CI.

4.2.2. THE EFFECT OF LOW PNP ON THE SURGICAL WORKSPACE SCALE

The SWS was lower in the low Pnp group (3.9, 95% CI 3.9-4.2) than in the standard Pnp group (4.2, 95% CI 4.0-4.4), but this difference was not statistically significant (p=0.07). The low Pnp group had higher blood loss than the standard Pnp group (mean 227 (SD 147.3) vs 159.9 (SD 110.4), p=0.01).

4.2.3. THE EFFECT OF LOW PNP ON THE URINARY KIDNEY INJURY MARKERS

Figure 4.3 illustrates the flow of patients.

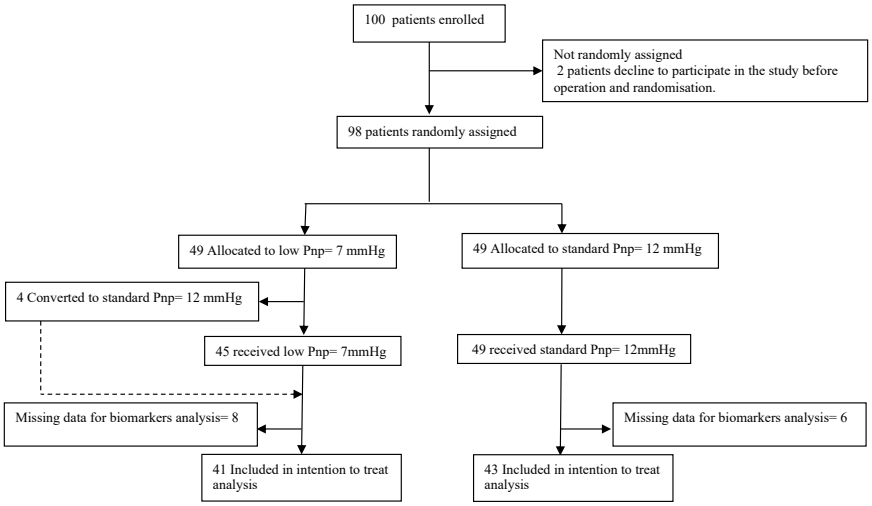

Figure 4.3 Patient Allocation and Follow-Up in the Study of AKI Biomarkers Following RARP: A CONSORT Flow Diagram

In the study investigating the impact of Pnp on u-NGAL levels following RARP, the mean u-NGAL level in the low Pnp group (7 mmHg) remained unchanged after surgery (22.8 ± 21.5 ng/ml) compared to before surgery (22.5 ± 35.2 ng/ml). Conversely, in the standard Pnp group (12 mmHg), there was a significant increase in u-NGAL levels postoperatively (60.9 ± 109.5 ng/ml) compared to preoperative levels (22.5 ± 35.2 ng/ml). The mean difference between the two groups was -39.9 ng/ml (95% CI: -73.7 to -6.1 ng/ml, p-value: 0.02). There is no significant difference observed in other renal injury markers, including KIM-1, VEGF, Osteoactivin, Clusterin, and Calbindin. [See Appendix C, Table 2 for the detailed value of urinary kidney injury markers both before and after surgery.]

4.2.4. SECONDARY OUTCOMES

The secondary outcomes from the three studies considered a variety of parameters.

The key secondary outcomes indicated that there were no significant differences between the low Pnp and standard Pnp groups in terms of oncological outcomes, time of surgery, length of hospital stay, and the occurrence of Clavien-Dindo grade complications, nor for post-operative morphine use, measured by MOE. [See Appendix B, Table 3, and the online supporting material for details on secondary surgical outcomes and complications, as reported using the Clavien-Dindo score.]

Intraoperative urine production was significantly different between the groups, with a median value of 200 ml (IQR: 100-325) in the low Pnp group compared to 100 ml (IQR: 50-200) in the standard Pnp group (p=0.01). Additionally, total postoperative urine production showed a significant increase in the low Pnp group, with a median of 1325 ml (IQR: 1025-1800) compared to 1000 ml (IQR: 850-1287) in the standard Pnp group (p=0.001). There was also a notable difference in 2-hour urine production post-surgery, recording a median of 300 ml (IQR: 200-500) in the low Pnp group as opposed to 200 ml (IQR: 100-300) in the standard Pnp group (p=0.0008). However, no significant difference was found in the volume of I.V. fluid infusion between the two groups. Other renal function parameters, urinary electrolytes, and the Albumin Creatinine Ratio (ACR) showed no significant differences. [See Appendix C, Table 3, 4 for additional renal function parameters and Urinary electrolyte analysis.]

The incidence of Acute Kidney Injury (AKI), as defined by KDIGO criteria, was evaluated among the patients. On the first postoperative day, stage 1 AKI was reported in 16 patients from the low Pnp group and 18 patients from the standard Pnp group. This difference was not statistically significant (p=0.67). Stage 2 AKI was less frequent on day one in the low Pnp group, affecting 2 patients versus 5 patients in the standard Pnp group, though this was not statistically significant (p=0.43). Ten days post-operation, there remained an equal number of patients with asymptomatic stage 1 AKI in both groups, 6, showing no significant variation between the groups (p=1.0). Considering the u-NGAL cutoff value previously established as predictive for AKI stage 2/3 at 78ng/ml,[57] our data indicated that 3 patients from the low Pnp group and 5 from the standard Pnp group progressed to AKI stage 2/3, but this difference was not statistically significant (p=0.73).

CHAPTER 5. DISCUSSION

5.1. STUDY 1 AND 2

This randomised controlled trial was designed to investigate the effect of low Pnp pressure on the quality of postoperative recovery, surgical workspace, and potential renal injury in patients undergoing RARP. To our knowledge, this study is the first to assess these outcomes in a RARP context, with both patient-reported and surgeon-reported measures being utilised alongside multiple markers of renal injury.

Our results demonstrate that low Pnp significantly improves the quality of postoperative recovery on the POD1, as measured by the QoR-15 questionnaire. There are no prior studies investigating the effect of low Pnp on the QoR after RARP specifically, and results from studies on other procedures are not conclusive. Studies on laparoscopic cholecystectomy and donor nephrectomy reported no differences in QoR between low and standard Pnp, whereas a large multicentric trial on colorectal surgery reported significant improvement in QoR with low Pnp.[41, 58, 59]

In the laparoscopic cholecystectomy study, the authors compared 10 mmHg versus 14 mmHg Pnp and observed no effect on QoR. This raises the question of whether 10 mmHg can indeed be considered 'low', and if the results might be due to a relatively high Pnp even in the 'low' group.[41]

In the donor nephrectomy trial, 64 patients were randomised to 6 mmHg versus 12 mmHg Pnp, and again no difference in QoR was reported. However, it should be noted that a significant portion of patients in the 'low' group (24%) had to be converted to a higher Pnp, suggesting that the sample size might not have been large enough to draw a reliable conclusion.[58]

Contrarily, a large multicentric trial investigating the impact of low Pnp during colorectal surgery demonstrated a significant improvement in the total QoR score, with additional improvements in comfort, physical independence, and pain domains. This supports our finding that low Pnp can enhance postoperative recovery, albeit in a different surgical context.[59]

In our trial, patients who underwent RARP with low Pnp experienced notable reductions in pain and demonstrated improvements in physical comfort and emotional state on the first postoperative day (POD1), according to a sub-analysis of the QoR-15 domains. These findings echo those of the large multicenter trial on colorectal surgery, extending such observations to RARP.

Complementing our results, Abaza et al. reported improved pain scores in a randomised study where RARP was performed under lower Pnp.[56].

Notably, studies investigating the impact of low Pnp in urological procedures are somewhat sparse. A recent systemic review identified only ten studies exploring the effects of low Pnp during live donor nephrectomy, prostatectomy, partial nephrectomy, and various benign upper tract procedures.[60], Meanwhile, a meta-analysis specifically on RARP included four retrospective studies.[55]. Contrastingly, the impact of low Pnp has been extensively studied within general surgical procedures. A meta-analysis encompassing 44 randomised clinical trials on low Pnp during elective cholecystectomy discovered that pain levels were significantly reduced at several points postoperatively (1st, 4th, 8th, 12th, and 24th hours) in patients who underwent the procedure with low Pnp. However, pain levels on the second and third postoperative days were less frequently investigated, with those studies that did address this timeline finding no significant differences.[61] These findings, along with our own results, underline the significant impact of low Pnp on postoperative pain, particularly on the first postoperative day. This period is crucial for the patient's recovery trajectory and plays a decisive role in the timeline for potential early hospital discharge.

In terms of other outcomes, such as total surgical duration, positive surgical margins, and Clavien-Dindo complications, our findings are consistent with the meta-analysis results, demonstrating no significant discrepancies. These results further validate that utilising low Pnp does not negatively impact these specific surgical outcomes.[55]

Our study demonstrated that the low Pnp group experienced slightly higher blood loss with a mean difference of approximately 67 ml. While this difference reached statistical significance, it's salient to consider its clinical relevance as it didn't translate into a meaningful impact on patients' postoperative outcomes nor necessitate blood transfusion interventions. This observed variance in blood loss contrasts with the results gleaned from the meta-analysis and the two independent randomised trials identified during our literature review, both of which reported no significant difference in blood loss between the standard and low Pnp groups.[11, 55, 56]

A plausible explanation for the increased blood loss in the low Pnp group may be linked to our surgical protocol; in our study, we recommended surgeons to maintain the assigned Pnp even during the dissection of the Dorsal Venous Complex (DVC), a surgical step which is conventionally associated with increased bleeding and often managed by a temporary increase in Pnp. Intriguingly, Ferroni et al. reported a similar trend in their retrospective study, with increased blood loss observed during RARP. [39] Although they did not directly measure intraoperative urine production, they noted an increased volume of urine entering the operative field. This led to speculation

that the difference in measured blood loss from the suction canisters may have, in part, resulted from a higher urine output during surgery under low Pnp. The increased urine production observed in our study during and after surgery may have contributed similarly to the measured blood loss.

The risk of post-operative ileus (POI) remains a contentious issue. Meta-analysis showed a significant reduction in POI risk under low Pnp conditions during RARP.[55] Despite this, the two randomised trials reported no significant variation in POI incidence, though earlier passing of flatus was noted in one trial among the low Pnp group.[11, 56] In alignment with these trials, our study found no substantial differences in POI occurrence between the groups, with POI developing in a single patient from the control group.

Upon the successful validation of the SWS, the implementation of our randomised trial proceeded with assurance. The validation study affirmed the reliability of the SWS, which, consistent with our trial, revealed no significant difference in workspace conditions between low and standard Pnp. This persistent performance of the scale across both studies underscores its validity and applicability in the realm of robotic surgery research.

However, the literature yields inconsistent results concerning the impact of low Pnp on the surgical workspace. Mahajan et al. pursued an objective evaluation of low Pnp during laparoscopic cholecystectomy, observing the contact between the parietal peritoneum and underlying organs during secondary port insertion. Despite this meticulous methodology, their findings discerned no notable differences in the visual contact between the parietal peritoneum and underlying viscera, suggesting that both pressure levels furnished a satisfactory surgical workspace and exposure.[62]

In a study by Rohloff et al., investigating the impact of low Pnp during RARP on POI, their trial involved 201 patients randomised to either 12 or 8 mmHg. Notably, no circumstances arose during the surgery necessitating an increase in the Pnp due to visibility issues. Interestingly, by the end of the operation, the surgeon was only able to correctly guess the Pnp assigned to the low Pnp arm 45% of the time, indirectly suggesting no difference in or satisfaction with the workspace.[11] Contrarily, a study by Barrio et al., assessing the influence of neuromuscular blockade (NMB) on surgical conditions during low-Pnp laparoscopic cholecystectomy, employed a four-step scale to evaluate surgical conditions at various time points. While their scale was not validated, their results suggested that surgical conditions during low-Pnp were not significantly enhanced by the depth of NMB, and that surgical conditions under standard Pnp were deemed superior, regardless of the NMB depth.[63] In a single-

centre randomised controlled trial with the primary outcome being quality of recovery, the surgical workspace during laparoscopic donor nephrectomy was evaluated every 15 minutes using the Leiden-Surgical Rating Scale (L-SRS). The study involved 64 live kidney donors, randomised to either 6 or 12 mmHg insufflation pressure. Interestingly, a considerable number of surgeries (24%) initially started under low Pnp and needed to convert to standard Pnp. The authors attributed this trend to a learning curve tied to operating under lower Pnp. After 30 minutes of insufflation, surgeries conducted under standard Pnp more frequently achieved an L-SRS score of 5, indicative of optimal conditions, compared to those performed under low Pnp. Nonetheless, it should be pointed out that the authors reported differences only for optimal conditions (L-SRS score of 5), without detailing the distribution of other L-SRS scores, which somewhat hampers a comprehensive comparison with our trial.[41]

In conclusion, although our randomised trial, leveraging the validated SWS, observed no significant difference in workspace conditions between low and standard Pnp, the literature presents diverse findings. These studies underline the potential influence of factors such as surgeon experience and adaptability when operating under lower Pnp. Further studies, preferably with validated scales, are warranted to shed more light on the impact of low Pnp on surgical workspace and, consequently, patient outcomes.

5.2. STUDY 3

In the last study, we examined the effect of low Pnp on renal function and renal injury biomarkers using various parameters. Although we detected a statistically significant difference in u-NGAL levels between the low Pnp and standard Pnp groups, the clinical significance of this finding may be limited. This is due to the fact that level in standard Pnp group remained below the previously reported AKI prediction cut-off value of 78 ng/ml. [57]

NGAL, a 25 kDa protein, is chiefly produced by the epithelia of damaged nephrons and has come to the fore as a potentially significant marker of renal epithelial injury. In contrast to serum creatinine and urinary output, general indicators of kidney function, NGAL is specifically upregulated within affected nephrons. Following this upregulation, it is released into the bloodstream and urine, allowing for its convenient detection and measurement.[29]

Our results seem to be at odds with those reported by two separate randomised studies which investigated the effect of low Pnp on NGAL levels. Filho et al. conducted a randomised study to assess the impact of low Pnp during laparoscopic cholecystectomy. Patients were randomly allocated to either a standard (10-12 mmHg) or a low Pnp group (6-8 mmHg). The study tracked changes in plasma NGAL

and cystatin C levels at three time points: beginning and end of the procedure and 24 hours later. Upon completion, data revealed no significant difference in the renal biomarkers between the two groups, but a substantial increase was observed over time, specifically at the end of the procedure. The study concluded that Pnp during laparoscopic cholecystectomy raises NGAL and cystatin C levels intraoperatively, but the use of low Pnp doesn't alter these biomarkers' patterns.[64]

Filho et al.'s study and our investigation reveal different impacts of Pnp on NGAL levels. This discrepancy might be explained by the different durations of exposure to Pnp. While Filho et al. reported a Pnp duration of 70 minutes for the standard Pnp group and 77 minutes for the low Pnp group during their laparoscopic cholecystectomy, our study entailed a more intricate radical operation, with a Pnp duration of 152 minutes for the standard Pnp group and 156 minutes for the low Pnp group.

Animal studies suggest a strong correlation between increased NGAL levels and extended Pnp exposure time. For instance, a study conducted on rats showed significant increases in NGAL levels beginning after the second hour of exposure to Pnp, which supports our findings. The increase was more prominent at high Pnp, and while no changes were observed in serum creatinine levels, novel markers like NGAL showed a clear response to prolonged Pnp.[65] Similarly, another research reported that NGAL level increased in direct correlation with the duration of Pnp, highlighting these biomarkers' sensitivity in detecting renal injury.[66]

Further, another randomised trial involving 20 patients who underwent donor nephrectomy presented similar findings. Patients were randomised to two groups subjected to 7mmHg and 14mmHg Pnp, respectively. Results displayed a gradual rise in u-NGAL, peaking on the second or third day, and in some instances, remained elevated 4-6 weeks post-procedure in both groups. The authors hypothesised that the observed damage could be attributed to alterations in blood supply, possibly mediated by renal reflexes, to the remaining kidney. Alternatively, it was suggested that nephrectomy might cause hypertrophy and dedifferentiation of tubular cells in the remaining kidney. This might result in a limited reabsorption capacity, leading to increased urinary excretion of otherwise reabsorbed low molecular weight proteins. Consequently, the elevated NGAL levels in both groups were attributed more to the procedure rather than the Pnp.[67]

In light of these studies, it is reasonable to infer that the increased complexity and extended duration of the RARP procedure in our study may explain the differences observed in u-NGAL levels.

In our study, the standard Pnp group demonstrated a significant decrease in intra- and postoperative urine production, which may imply a transient renal injury. These observations could be linked to the direct and indirect effects of Pnp, which we explored in Chapter 1 (page 19, section 1.2). It's crucial to note that research suggests these physiological changes typically start when Pnp exceeds 10 mmHg. [19]This might imply that Pnp levels below 10 mmHg may not significantly affect renal physiology, leading us to question whether low Pnp (below 10 mmHg) in our study may have mitigated the effects on urine production and potential renal injury.

The results from NGAL align well with the definitions of stages 2/3 AKI according to the KDIGO criteria,[22] bolstering the credibility of u-NGAL as a predictive biomarker for these AKI stages. However, it is crucial to interpret these results with care. The absence of a significant difference in the KDIGO-defined AKI between the two groups suggests that the observed variation in u-NGAL levels may not significantly impact overall renal function or clinical outcomes.

We observed no changes in other renal injury markers, including calbindin, clusterin, KIM-1, osteoactivin (OA), and VEGF, which are known to indicate kidney damage and show elevated levels in urine across various kidney disorders. [68, 69]

Previous research has shown urinary calbindin levels to be a reliable indicator of AKI, [69, 70] being linked to distal tubular cell damage and showing increased expression in vitro after exposure to certain agents, such as cisplatin.[71] Similarly, OA, also known as glycoprotein non-melanoma clone B (gpnmb), plays a crucial role in the differentiation and functioning of various cell types, with its therapeutic potential being explored in tissue regeneration for bone, liver, muscle, and kidney injuries.[72] The high expression of OA in the renal interstitial and tubular epithelial cells was detected in an animal model following unilateral ureteral obstruction.[73]

When AKI occurs due to intrinsic renal causes, substantial proximal tubular injury can result. This damage might impede the ability of the proximal tubule to reabsorb albumin, which can cause albuminuria.[25] Earlier studies have indicated that the u-ACR is a sensitive indicator for identifying AKI, and it might forecast the risk of AKI sooner than serum creatinine levels alone.[74, 75]

The insights gained from the current research suggest that the clinical application of low Pnp during RARP warrants further investigation. Observing diminished u-NGAL levels in the low Pnp group might imply that low Pnp has a role in reducing renal

injury and enhancing recovery. However, the lack of a significant distinction in the gold standard AKI definition by KDIGO across the two groups suggests that the clinical influence might be limited. It would be of interest to ascertain whether certain patient groups, like those with existing renal conditions, may gain greater benefits from low Pnp during RARP, or, indeed, during more complex and lengthy procedures such as radical cystectomy.

CHAPTER 6. LIMITATION AND FUTURE RESEARCH

While our research offers meaningful insights into the impact of low Pnp on quality of recovery, surgical workspace, and renal function during robot-assisted radical prostatectomy (RARP), several limitations need to be acknowledged.

A major limitation of our study is its single-institution nature. All surgeries were performed by only two high-volume surgeons, which may potentially affect the generalisability of our findings. Our results may not be directly applicable to less experienced surgeons, particularly considering the potential risk of increased bleeding in these cases. Thus, multi-institutional studies incorporating a broader range of surgeon experiences are warranted to verify the applicability of our findings on a larger scale.

In regards to the renal function study, the follow-up duration is a crucial limitation. Our study design enabled the detection of immediate post-operative changes in renal function, but it did not capture insights into potential long-term effects of low Pnp on renal health. Given that renal injury can manifest delayed effects and the recovery or deterioration of renal function can be a prolonged process, the short follow-up period might potentially limit our understanding of the chronic implications of low Pnp during RARP. Therefore, future investigations should include extended follow-up periods to identify potential long-term effects of low Pnp on renal function.

Despite these limitations, our studies contribute to a growing body of evidence supporting the use of low Pnp during minimally invasive surgery. Future research need to focus on addressing these limitations with multi-institutional trials. Such investigations will be instrumental in understanding the broader implications of low Pnp, potentially leading to more nuanced surgical guidelines and improved patient outcomes.

CHAPTER 7. CONCLUSSION

The culmination of our studies presents compelling evidence that low pneumoperitoneum (Pnp) can be employed effectively and safely in robot-assisted radical prostatectomy (RARP) without compromising surgical workspace or increasing clinically significant blood loss.

Our findings indicate that the use of low Pnp may promote better postoperative recovery, as demonstrated by the improved quality of recovery scores. This is a crucial insight, contributing to the patient-centric approach to surgical outcomes, where postoperative recovery is as significant as surgical success.

Importantly, our studies challenge the traditional assumption, unsupported by empirical evidence, that low Pnp might limit the surgical workspace. Our data do not suggest any compromise to the surgeon's workspace when lower Pnp are used, underscoring the need for surgical practices to be guided by scientific evidence rather than tradition alone.

Additionally, we explored the effects of low Pnp on renal function, focusing on the biomarker neutrophil gelatinase-associated lipocalin (NGAL). We noted a statistically significant decrease in urinary NGAL (u-NGAL) levels in the low Pnp group. Though the clinical implications of this finding may be limited due to the overall absence of significant differences in acute kidney injury (AKI) as defined by the gold standard KDIGO criteria, it does provide a hint that low Pnp might have a role in reducing renal injury. However, these potential benefits warrant further exploration in future research.

In conclusion, our collective findings point towards the potential advantages of employing low Pnp during RARP, particularly in enhancing postoperative recovery and possibly reducing renal injury. It is essential to continue building upon this body of evidence through further research, ultimately leading to improved surgical protocols and better patient outcomes. As we move forward, the application of low Pnp during RARP and other more complex, longer surgical procedures may benefit from the findings of our research.

CHAPTER 8. LITERATURE LIST

[1] Hatzinger M, Kwon ST, Langbein S, et al. Epochs in Endourology Hans Christian Jacobaeus : *J Endourol* 2006; 20: 848–850.

[2] Cheng Y, Lu J, Xiong X, et al. Gases surgery estabilishing pneumoperitoneum during laparoscopic abdominal surgery (Review). *Cochrane Database Syst Rev*. Epub ahead of print 2013. DOI: 10.1002/14651858.CD009569.pub3.www.cochranelibrary.com.

[3] S E A Attwood, K Mealy RBS. prospective comparison of laparoscopic versus open cholecystectomy Senior Registrar in Surgery Senior Registrar in Surgery. 1992; 74: 397–400.

[4] Martínez-Pérez A, Carra MC, Brunetti F, et al. Short-term clinical outcomes of laparoscopic vs open rectal excision for rectal cancer: A systematic review and metaanalysis. *World J Gastroenterol* 2017; 23: 7906–7916.

[5] Coccolini F, Catena F, Pisano M, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. *Int J Surg* 2015; 18: 196–204.

[6] Atkinson TM, Giraud GD, Togioka BM, et al. Cardiovascular and Ventilatory Consequences of Laparoscopic Surgery. *Circulation* 2017; 135: 700–710.

[7] Kashtan J, Green JF, Parsons EQ, et al. Hemodynamic effect of increased abdominal pressure. *J Surg Res* 1981; 30: 249–255.

[8] Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. *Surg Endosc Other Interv Tech* 2002; 16: 1121–1143.

[9] Hirvonen EA, Nuutinen LS, Vuolteenaho O. Hormonal responses and cardiac filling pressures in head-up or head-down position and pneumoperitoneum in patients undergoing operative laparoscopy. *Br J Anaesth* 1997; 78: 128–133.

[10] Tan M, Xu F-F, Peng J-S, et al. Changes in the level of serum liver enzymes after laparoscopic surgery. *World J Gastroenterol* 2003; 9: 364–367.

[11] Rohloff M, Peifer G, Shakuri-Rad J, et al. The impact of low pressure pneumoperitoneum in robotic assisted radical prostatectomy: a prospective, randomized, double blinded trial. *World J Urol* 2021; 39: 2469–2474.

[12] *EAES Guidelines for Endoscopic Surgery*. 2006. Epub ahead of print 2006. DOI: 10.1007/978-3-540-32784-4.

[13] Koivusalo AM, Kellokumpu I, Ristkari S, et al. Splanchnic and renal deterioration during and after laparoscopic cholecystectomy: a comparison of the carbon dioxide pneumoperitoneum and the abdominal wall lift method. *Anesth Analg* 1997; 85: 886–891.

[14] Khoury W, Jakowlev K, Fein A, et al. Renal Apoptosis Following Carbon Dioxide Pneumoperitoneum in a Rat Model. *J Urol* 2008; 180: 1554–1558.

[15] Seguro AC, Poli De Figueiredo LF, Shimizu MHM. N-acetylcysteine (NAC) protects against acute kidney injury (AKI) following prolonged pneumoperitoneum in the rat. *J Surg Res* 2012; 175: 312–315.

[16] Wiesenthal JD, Fazio LM, Perks AE, et al. Effect of pneumoperitoneum on renal tissue oxygenation and blood flow in a rat model. *Urology* 2011; 77: 1508.e9-1508.e15.

[17] O'Leary E, Hubbard K, Tormey W, et al. Laparoscopic cholecystectomy: haemodynamic and neuroendocrine responses after pneumoperitoneum and changes in position. *Br J Anaesth* 1996; 76: 640–644.

[18] Hazebroek EJ, de Vos tot Nederveen Cappel R, Gommers D, et al. Antidiuretic hormone release during laparoscopic donor nephrectomy. *Arch Surg* 2002; 137: 600–4; discussion 605.

[19] Sodha S, Nazarian S, Adshead JM, et al. Effect of Pneumoperitoneum on Renal Function and Physiology in Patients Undergoing Robotic Renal Surgery. *Curr Urol* 2016; 9: 1–4.

[20] Kopitkó C, Medve L, Gondos T, et al. Mediators of Regional Kidney Perfusion during Surgical Pneumo-Peritoneum Creation and the Risk of Acute Kidney Injury—A Review of Basic Physiology. *J Clin Med*; 11. Epub ahead of print 2022. DOI: 10.3390/jcm11102728.

[21] Wever KE, Bruintjes MHD, Warlé MC, et al. Renal Perfusion and Function during Pneumoperitoneum: A Systematic Review and Meta-Analysis of Animal Studies. *PLoS One* 2016; 11: e0163419.

[22] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; 120: c179-84.

[23] Kashani K, Rosner MH, Ostermann M. Creatinine: From physiology to

clinical application. *Eur J Intern Med* 2020; 72: 9–14.

[24] Levey AS, Perrone RD, Madias NE. Serum creatinine and renal function. *Annu Rev Med* 1988; 39: 465–490.

[25] Bolisetty S, Agarwal A. Urine albumin as a biomarker in acute kidney injury. *Am J Physiol - Ren Physiol* 2011; 300: 626–627.

[26] Eremina V, Baelde HJ, Quaggin SE. Role of the VEGF--a signaling pathway in the glomerulus: evidence for crosstalk between components of the glomerular filtration barrier. *Nephron Physiol* 2007; 106: p32-7.

[27] Iida T, Fujinaka H, Xu B, et al. Decreased urinary calbindin 1 levels in proteinuric rats and humans with distal nephron segment injuries. *Clin Exp Nephrol* 2014; 18: 432–443.

[28] Hemmingsen C. Regulation of renal calbindin-D28K. *Pharmacol Toxicol* 2000; 87 Suppl 3: 5–30.

[29] Singer E, Markó L, Paragas N, et al. Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications. *Acta Physiol (Oxf)* 2013; 207: 663–672.

[30] Bonventre J V. Kidney Injury Molecule-1 (KIM-1): a specific and sensitive biomarker of kidney injury. *Scand J Clin Lab Invest Suppl* 2008; 241: 78–83.

[31] Patel-chamberlin M, Wang Y, Satirapoj B, et al. Hematopoietic growth factor inducible neurokinin-1 (Gpnmb / Osteoactivin) is a biomarker of progressive renal injury across species. *Kidney Int* 2011; 79: 1138–1148.

[32] Hypólito OHM, Azevedo JLMC, De Lima Alvarenga Caldeira FMS, et al. Creation of pneumoperitoneum: Noninvasive monitoring of clinical effects of elevated intraperitoneal pressure for the insertion of the first trocar. *Surg Endosc* 2010; 24: 1663–1669.

[33] Boon M, Martini CH, Aarts LPHJ, et al. The use of surgical rating scales for the evaluation of surgical working conditions during laparoscopic surgery: a scoping review. *Surg Endosc* 2019; 33: 19–25.

[34] Martini CH, Boon M, Bevers RF, et al. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. *Br J Anaesth* 2014; 112: 498–505.

[35] Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of

a postoperative quality of recovery score: The QoR-15. *Anesthesiology* 2013; 118: 1332–1340.

[36] Kleif J, Edwards HM, Sort R, et al. Translation and validation of the Danish version of the postoperative quality of recovery score QoR-15. *Acta Anaesthesiol Scand* 2015; 59: 912–920.

[37] Gurusamy KS, Vaughan J, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. *Cochrane Database Syst Rev*; 2014. Epub ahead of print 2014. DOI: 10.1002/14651858.CD006930.pub3.

[38] Bogani G, Uccella S, Cromi A, et al. Low vs Standard Pneumoperitoneum Pressure During Laparoscopic Hysterectomy: Prospective Randomized Trial. *J Minim Invasive Gynecol* 2014; 21: 466–471.

[39] Ferroni MC, Abaza R. Feasibility of robot-assisted prostatectomy performed at ultra-low pneumoperitoneum pressure of 6 mmHg and comparison of clinical outcomes vs standard pressure of 15 mmHg. *BJU Int*. Epub ahead of print 1 August 2019. DOI: 10.1111/bju.14682.

[40] Rohloff M, Cicic A, Christensen C, et al. Reduction in postoperative ileus rates utilizing lower pressure pneumoperitoneum in robotic-assisted radical prostatectomy. *J Robot Surg*. Epub ahead of print 1 October 2019. DOI: 10.1007/s11701-018-00915-w.

[41] Özdemir-van Brunschot DMD, Scheffer GJ, van der Jagt M nbi., et al. Quality of Recovery After Low-Pressure Laparoscopic Donor Nephrectomy Facilitated by Deep Neuromuscular Blockade: A Randomized Controlled Study. *World J Surg* 2017; 41: 2950–2958.

[42] Warlé MC, Berkers AW, Langenhuijsen JF, et al. Low-pressure pneumoperitoneum during laparoscopic donor nephrectomy to optimize live donors' comfort. *Clin Transplant* 2013; 27: 478–483.

[43] Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012; 10: 28–55.

[44] Huynh LM, Ahlering TE. Robot-Assisted Radical Prostatectomy: A Step-by-Step Guide. *J Endourol* 2018; 32: S28–S32.

[45] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a

survey. *Ann Surg* 2004; 240: 205–213.

[46] Nielsen S, Degenhardt L, Hoban B, et al. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf* 2016; 25: 733–737.

[47] Cook CE. Clinimetrics Corner: The Minimal Clinically Important Change Score (MCID): A Necessary Pretense. *J Man Manip Ther* 2008; 16: E82-3.

[48] Ivry M, David G, Wiam W, et al. Melatonin premedication improves quality of recovery following bariatric surgery – a double blind placebo controlled prospective study. *Surg Obes Relat Dis* 2017; 13: 502–506.

[49] Torensma B, Martini CH, Boon M, et al. Deep neuromuscular block improves surgical conditions during bariatric surgery and reduces postoperative pain: A randomized double blind controlled trial. *PLoS One* 2016; 11: 1–14.

[50] Mose FH, Jörgensen AN, Vrist MH, et al. Effect of 3% saline and furosemide on biomarkers of kidney injury and renal tubular function and GFR in healthy subjects - A randomized controlled trial. *BMC Nephrol* 2019; 20: 1–14.

[51] Kancir ASP, Pleckaitiene L, Hansen TB, et al. Lack of nephrotoxicity by 6% hydroxyethyl starch 130/0.4 during hip arthroplasty: a randomized controlled trial. *Anesthesiology* 2014; 121: 948–958.

[52] Modarresi A, Nafar M, Sahraei Z, et al. N-acetylcysteine decreases urinary level of neutrophil gelatinase-associated lipocalin in deceased-donor renal transplant recipients: a randomized clinical trial. *Biomarkers Biochem Indic Expo response, susceptibility to Chem* 2018; 23: 589–596.

[53] J T, L B, T H, et al. Different ways to estimate treatment effects in randomised controlled trials. *Contemp Clin trials Commun* 2018; 10: 80–85.

[54] Alhusseinawi H, Haase R, Rasmussen S, et al. Validation of a surgical workspace scale during robot-assisted surgery. *Int J Med Robot Comput Assist Surg* 2023; 19: 5–8.

[55] El-Taji O, Howell-Etienne J, Taktak S, et al. Lower vs standard pressure pneumoperitoneum in robotic-assisted radical prostatectomy: a systematic review and meta-analysis. *J Robot Surg*. Epub ahead of print 2022. DOI: 10.1007/s11701-022-01445-2.

[56] Abaza R, Ferroni MC. Randomized Trial of Ultralow vs Standard Pneumoperitoneum during Robotic Prostatectomy. *J Urol* 2022; 208: 626–

632.

[57] Tecson KM, Erhardtsen E, Eriksen PM, et al. Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: Retrospective determination and clinical validation of a prospective multicentre study. *BMJ Open* 2017; 7: 1–8.

[58] Moro ET, Pinto PCC, Neto AJMM, et al. Quality of recovery in patients under low- or standard-pressure pneumoperitoneum. A randomised controlled trial. *Acta Anaesthesiol Scand* 2021; 65: 1240–1247.

[59] Albers KI, Polat F, Helder L, et al. Quality of Recovery and Innate Immune Homeostasis in Patients Undergoing Low-pressure Versus Standard-pressure Pneumoperitoneum During Laparoscopic Colorectal Surgery (RECOVER): A Randomized Controlled Trial. *Ann Surg* 2022; 276: e664–e673.

[60] West A, Hayes J, Bernstein DE, et al. Clinical outcomes of low-pressure pneumoperitoneum in minimally invasive urological surgery. *J Robot Surg* 2022; 16: 1183–1192.

[61] Ortenzi M, Montori G, Sartori A, et al. Low-pressure versus standard-pressure pneumoperitoneum in laparoscopic cholecystectomy: a systematic review and meta-analysis of randomized controlled trials. *Surg Endosc* 2022; 36: 7092–7113.

[62] Mahajan S, Shankar M, Garg VK, et al. Intraoperative safety of low pressure pneumoperitoneum cholecystectomy: a comparative study. *Int Surg J* 2017; 4: 3679.

[63] Barrio J, Errando CL, García-Ramón J, et al. Influence of depth of neuromuscular blockade on surgical conditions during low-pressure pneumoperitoneum laparoscopic cholecystectomy: A randomized blinded study. *J Clin Anesth* 2017; 42: 26–30.

[64] Marton Filho MA, Alves RL, Nascimento P do J, et al. Effects of pneumoperitoneum on kidney injury biomarkers: A randomized clinical trial. *PLoS One* 2021; 16: e0247088.

[65] Kozan R, Şare M, Yılmaz TU, et al. Effectiveness of new parameters in the evaluation of pneumoperitoneum-related acute kidney injury in rats. *Turkish J Med Sci* 2018; 48: 1278–1284.

[66] Yildirim D, Donmez T, Sunamak O, et al. The effects of prolonged CO2

insufflation on kidney function in a rat pneumoperitoneum model. *Wideochirurgia i inne Tech maloinwazyjne = Videosurgery other miniinvasive Tech* 2017; 12: 125–134.

[67] Hoogendijk-Van Den Akker JM, Warlé MC, Van Zuilen AD, et al. Urinary biomarkers after donor nephrectomy. *Transpl Int* 2015; 28: 544–552.

[68] Brott DA, Adler SH, Arani R, et al. Characterization of renal biomarkers for use in clinical trials: biomarker evaluation in healthy volunteers. *Drug Des Devel Ther* 2014; 8: 227–237.

[69] Won AJ, Kim S, Kim YG, et al. Discovery of urinary metabolomic biomarkers for early detection of acute kidney injury. *Mol Biosyst* 2016; 12: 133–144.

[70] Lane BR, Babitz SK, Vlasakova K, et al. Evaluation of Urinary Renal Biomarkers for Early Prediction of Acute Kidney Injury Following Partial Nephrectomy: A Feasibility Study. *Eur Urol Focus* 2020; 6: 1240–1247.

[71] Takashi M, Zhu Y, Miyake K, et al. Urinary 28-kD calbindin-D as a new marker for damage to distal renal tubules caused by cisplatin-based chemotherapy. *Urol Int* 1996; 56: 174–179.

[72] Huang Y, Bai B, Yao Y. Prospects of osteoactivin in tissue regeneration. *Expert Opin Ther Targets* 2016; 20: 1357–1364.

[73] Nakamura A, Ishii A, Ohata C, et al. Early induction of osteoactivin expression in rat renal tubular epithelial cells after unilateral ureteral obstruction. *Exp Toxicol Pathol Off J Gesellschaft fur Toxikologische Pathol* 2007; 59: 53–59.

[74] Zappitelli M, Coca SG, Garg AX, et al. The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. *Clin J Am Soc Nephrol* 2012; 7: 1761–1769.

[75] Schnabel K, Garam N, Ledó N, et al. Urinary albumin-to-creatinine ratio and serum albumin are predictors of acute kidney injury in non-ventilated COVID-19 patients: a single-center prospective cohort study. *Int Urol Nephrol* 2023; 55: 711–720.

CHAPTER 9. APPENDICES

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ORIGINAL ARTICLE

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Validation of a surgical workspace scale during robot-assisted surgery

Hayder Alhusseinawi[1,2] | Rikke Haase[1] | Sten Rasmussen[1,2] | Jørgen B. Jensen[3,4] | Pernille S. Kingo[3,4]

[1]Department of Urology, Aalborg University Hospital, Aalborg, Denmark

[2]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

[3]Department of Urology, Aarhus University Hospital, Aarhus, Denmark

[4]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Correspondence

Hayder Alhusseinawi, Department of Urology, Aalborg University Hospital, Aalborg, Denmark.

Email: alhusseinawi.h@gmail.com

Abstract

Background: A sufficient surgical workspace is crucial to avoid complications. Within classic laparoscopy, many subjective surgical rating scales (SRSs) have previously been used to evaluate the surgical workspace. This study aimed to validate a modified version of the 5-point SRS during robot-assisted radical nephrectomy (RARN).

Methods: Thirty-two intra-operative videos of intraperitoneal spaces were recorded from eight patients who underwent RARN. To attain the visualisation of different types of workspaces, we recorded 20 s panoramic videos of different pneumoperitoneum, namely 3, 5, 7 and 12 mmHg. The videos were randomised and presented two times to eight experienced robotic surgeons to evaluate the workspace using our modified 5-point SRS. Both inter-and intra-rater reliabilities were tested.

Results: The results of the validation study showed moderate inter-rater and good to excellent intra-rater reliability.

Conclusion: This is a valid tool that can be confidently used by future researchers in the field of robot-assisted surgery.

KEYWORDS

computer assisted surgery, kidney, minimal invasive surgery, nephrectomy, robot assisted surgery, surgical rating scale, urology, validation study, workspace

1 | INTRODUCTION

A safe and successful robot-assisted laparoscopic surgery is dependent on creating a workspace in the abdominal cavity to allow for adequate visualisation and sufficient room for manipulation of laparoscopic instruments during the surgical procedure. This is achieved through the establishment of pneumoperitoneum (PnP) using carbon dioxide. PnP facilitates laparoscopy by expanding the abdominal cavity and suppressing the bowels and viscera, thereby giving the laparoscopic surgeon a good intra-operative view and unhindered manoeuvrability. During the surgery, the surgeon adjusts the PnP and muscle relaxation status together with the anaesthetist to ensure the best workspace throughout the surgery.

Many subjective surgical rating scales (SRSs) have been designed to evaluate the workspace and different interventions proposed to improve it. Boon and colleagues presented 17 different rating scales in their review, but most of them lack a validation test.[1]

A 5-point SRS was used in laparoscopic herniotomy, prostatectomy and nephrectomy in two different studies. In these studies it was suggested by the authors that increasing the depth of muscle relaxation and/or increasing PnP and changing the position of the patient or surgeon could improve the workspace.[2,3]

Robot-assisted surgery (RAS) is rapidly expanding within the surgical field making it possible to perform longer and more complex procedures. The 5-point SRS originally designed for classical laparoscopic surgery, and the item and adjustment suggested by the 5-point SRS authors no longer fit the current RAS circumstances. Therefore, it is essential to design a more suited SRS for RAS.

With this study, we aimed to validate a modified 5-point categorial SRS to be used in future studies where the intervention that affects the workspace is a matter of concern during RAS.

2 | MATERIAL AND METHODS

2.1 | Surgical workspace scale

Our workspace scale was re-designed from the previously described SRSs to fit RAS.[2,3] The appraisal score used to grade the SRS length proposed by Boon et al. was used to determine the best-suited surgical workspace scale.[1] By including five adequately defined items, testing both inter-and intra-rater reliability and correlating the workspace to the muscle relaxation and/or PnP status, our scale reached a score of 5/5.

The scale was designed in cooperation with a high-volume robotic surgeon. We tried to keep the scale as simple as possible, taking the advantages and limitations of robotic surgeries into consideration and ensuring that the scale would be applicable to future studies. The main qualitative topics were kept unchanged, namely the extremely poor, very poor, acceptable, good and optimal conditions adopted from the previously described Leiden SRS scale used in laparoscopic surgery.[3] The suggested interventions in our study consisted of adjustments for muscle relaxation, PnP, assessment of gas leakage and specific direct guidance of bedside assistants was added by our surgeon (R.H.). Our modified surgical workspace scale is described in Table 1.

2.2 | Design and inclusion criteria

The study was designed as a prospective cohort study. The study was conducted at a single tertiary urological cancer centre and included all patients above 18 years of age diagnosed with renal tumours who underwent radical nephrectomy from February 2021 to April 2021. Patients with a body mass index >35 kg/m^2 and/or a previous history of open abdominal surgery were excluded from the study.

2.3 | Video recording

Thirty-two videos from eight patients who met the inclusion criteria were recorded. A 20-s panoramic video was systematically recorded four times during each surgery. After establishing PnP and placement of ports, the PnP pressure decreased to 3 mmHg in furtherance of the worst possible workspace. The PnP was consecutively raised to 5, 7 and 12 mmHg. A new video was recorded with each new pressure. We aimed to simulate the full range of workspace conditions by changing the PnP level. The recorded videos were then duplicated, randomised and embedded in an online survey. Eight experienced robotic surgeons (all consultants in urology and sub-specialised in onco-urology) from two high-volume centres assessed the videos using the surgical workspace scale through an online survey. An example of the video recordings can be seen on https://vimeo.com/660265156.

2.4 | Statistics

For the study statistics, StataCorp. 2021, Stata Statistical Software, ver. 17. College Station, TX: StataCorp LLC was used.

TABLE 1 The surgical workspace scale

1. *Extremely poor conditions*: The surgeon is unable to work due to the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation or low intra-abdominal pressure. Additional muscle relaxants must be given, or intra-abdominal pressure should be increased
2. *Poor conditions*: There is a visible laparoscopic field, but the surgeon is severely hampered by small room with the hazard of tissue damage. Additional muscle relaxants must be given, or intra-abdominal pressure should be increased
3. *Acceptable conditions*: There is a wide visible laparoscopic field, but still some interference with the surgeon's work. After **one or two** minor adjustments surgery can be completed
4. *Good conditions*: There is a wide laparoscopic working field, but there is some interference, but no need for adjustments
5. *Optimal conditions*: The laparoscopic working field is optimal, and procedure can be completed without any interference

Minor intervention
1. Asses the possibility of gas leakage
2. Specific direct guidance of assistance
3. Assess relaxation status with anaesthetist

The precision approach was used to determine the sample size.[4,5] Using the sample size determination approach described by Bonett[6] and assuming an inter-class correlation coefficient (ICC) = 0.80, eight raters and a 95% confidence interval (CI) around ICC of width (0.2) gave a sample size of $n = 25$ records where each record was regarded as an individual subject (seven patients). Given a predicted dropout of 10% due to possible damage to recorded videos or poor-quality recordings, eight patients were included (32 records).

Although the equivalence of results from the ICC and weighted kappa tests has been previously described,[7] the research group considered running both statistical methods.

To assess the inter-rater reliability, we used a two-way random-effect model with absolute agreement ICC and a Fleiss weighted (quadratic) kappa. To test intra-rater reliability (test-retest), we used a two-way mixed-effect model with absolute agreement ICC.

The following classifications have been suggested by Koo et al. for assessing how good the strength of agreement is based on the value of the ICC. Values <0.5 indicate poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability and values >0.90 indicate excellent reliability.[8]

2.5 | Ethics

This study was conducted according to the national guidelines on reporting clinical trials and was approved by the institutional review board and the research ethical committee in the Northern Region of Jutland (Protocol No. N-20200078, approval date 08 December 2020). All patients received both oral and written information about the study and signed consent was obtained.

3 | RESULTS

Patient demographics are shown in Table 2.

TABLE 2 Demographics of eight patients who underwent RARN due to renal cancer

Age	58 (49–64)
Sex	
Male	5 (62.5%)
Female	3 (37.5%)
BMI	24.3 (±4)
DM	3 (37%)
Hypertension	2 (25%)

Note: Data are mean (SD), *n* (%), or median (IQR).

Abbreviations: BMI, body mass index; DM, diabetes mellitus; RARN, robot-assisted radical nephrectomy.

One video record was excluded due to technical damage.

The pooled inter-rater agreement between surgeons showed moderate reliability with an ICC of 0.74 95% CI (0.66–81) with a slight difference between the first and second evaluations. Results from the weighted Fliess kappa test are shown in Table 3.

The intra-rater reliability (test-retest) of eight surgeons shows good to excellent reliability. The ICC and 95% CI ranged between 0.80 (0.62–0.89) and 0.98 (0.97–0.99) and the pooled ICC was 0.89 (0.86–91).

The ICC and CI of the surgical workspace scale for all surgeons are shown in Table 4. All surgeons used the full-scale range from 1 to 5 at almost the same frequency; however, they used item 3 more frequently than the other scale items (30%).

The surgeons changed their rating approximately seven times between the first and second evaluations. Among all surgeons a total of 53 changes were made.

TABLE 3 Inter-rater reliability of eight surgeons assessing workspace of 31 recorded videos

First evaluation		
Inter-rater reliability tested by Fleiss kappa	0.75	95% CI (0.63–0.87)
Inter-rater reliability tested by ICC	0.76	95% CI (0.64–0.85)
Second evaluation		
Inter-rater reliability tested by Fleiss kappa	0.72	95% CI (0.60–0.84)
Inter-rater reliability tested by ICC	0.73	95% CI (0.62–0.83)

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient.

TABLE 4 Intra-rater reliability of surgical workspace scale for eight surgeons

Raters (surgeons) number	ICC	95% CI
1	0.90	0.81–0.95
2	0.92	0.84–0.96
3	0.83	0.62–0.92
4	0.90	0.81–0.95
5	0.82	0.64–0.91
6	0.80	0.62–0.89
7	0.88	0.77–0.94
8	0.98	0.97–0.99
The pooled reliability	0.89	0.86–0.91

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient.

4 | DISCUSSION

This is the first prospective observational study that aimed to validate the surgical workspace scale to be used for robotic surgery studies, especially where the assessment of the surgical workspace is the outcome of focus during the implementation of new techniques or measures. This study showed moderate inter-rater and good to excellent intra-rater reliability.

Throughout the years, many different SRSs have been designed. As previously mentioned, most of these scales lacked validation.[1]

Martini et al. developed their 5-point Leiden-surgical rating scale for laparoscopic urologic surgery.[3] The scale items are well-described and incorporate visibility of critical structures, working space and muscle contractions as determinants of the surgical working field. They tested the workspace to compare deep versus moderate muscle relaxation, focussing on muscle contraction and relaxation as a parameter for scoring without considering PnP. The scale was tested for inter-rater reliability by comparing the rating score of the operating surgeon with the rating score of 12 anaesthesiologists, finding poor agreement. The authors attributed the results to anaesthesiologists being less capable of evaluating surgical conditions during laparoscopy from video images and hence deriving insufficient information from these images regarding the working conditions of the surgeon. Hence, a 30-s video image does not provide sufficient input to assess the quality of surgical conditions in non-surgically skilled personnel.

Furthermore, in a study by Nervil et al. using another design for a 5-point SRS, the researchers assessed both inter-and intra-rater reliabilities.[2] The studies showed fair inter-rater agreement but an excellent intra-rater agreement.

The study has several strengths, including the use of the full range of the scale (1–5) during the evaluation process. The detailed description of scale points with flexibilities of possible major and minor interventions decreased the variability between the raters, which could be the reason why our scale has higher inter-rater reliability compared to previous similar studies. We recruited eight robotic surgeons within onco-urology from two high-volume robotic centres. Every surgeon had performed at least 200 robotic surgeries before the time of recruitment to add to the solidity and credibility of our results.

The major limitation of this study is a subjective evaluation of the workspace that is difficult to prevent. The definition of acceptable workspace could differ for different surgeons. While some surgeons evaluated the low Pnp (7 mmHg) as an acceptable workspace other surgeons scored both low and ultra-low Pnp (5 mmHg) as acceptable. This is well presented in our data as item 3 of the scale that refer to the acceptable workspace was the most frequently used item. The other limitation reported by some of the surgeons who evaluated the video was the absence of surgical instruments and tissue handling, which led to the inaccurate evaluation of some videos. Therefore, when the surgical workspace scale is used in future studies, we recommend using the scale multiple times during the surgery in the predefined steps of the surgical procedure, which could be challenging for a surgeon in terms of workspace.

5 | CONCLUSION

The modified workspace scale described here shows moderate inter-rater and good to excellent intra-rater reliability. Therefore, it is a valid tool that can be confidently used by future researchers in the field of RAS.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Hayder Alhusseinawi https://orcid.org/0000-0002-2170-3771

REFERENCES

1. Boon M, Martini CH, Aarts LPHJ, Dahan A. The use of surgical rating scales for the evaluation of surgical working conditions during laparoscopic surgery: a scoping review. *Surg Endosc*. 2019;33(1):19-25. https://doi.org/10.1007/s00464-018-6424-5
2. Nervil GG, Medici R, Thomsen JLD, et al. Validation of subjective rating scales for assessment of surgical workspace during laparoscopy. *Acta Anaesthesiol Scand*. 2017;61(10):1270-1277. https://doi.org/10.1111/aas.13001
3. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. *Br J Anaesth*. 2014;112(3):498-505. https://doi.org/10.1093/bja/aet377
4. Bristol DR. Sample sizes for constructing confidence intervals and testing hypotheses. *Stat Med*. 1989;8(7):803-811. https://doi.org/10.1002/sim.4780080705
5. Chow S-C, Wang H, Shao J. *Sample Size Calculations in Clinical Research*. 2nd ed. Chapman & Hall/CRC; 2007. https://doi.org/10.1201/9781584889830
6. Bonett DG. Sample size requirements for estimating intraclass correlations with desired precision. *Stat Med*. 2002;21(9):1331-1335. https://doi.org/10.1002/sim.1108
7. Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. *Educ Psychol Meas*. 1973;33(3):613-619. https://doi.org/10.1177/001316447303300309
8. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med*. 2016;15(2):155-163. https://doi.org/10.1016/j.jcm.2016.02.012

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Appendix B. Paper 2

Original Article

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Low- versus standard- pneumoperitoneum in patients undergoing robot-assisted radical prostatectomy: a randomised, triple-blinded study

Hayder Alhusseinawi[1,2], Lotte Sander[2], Pernille M. Rosenvinge[1], Sarah L. Jensen[1], Niels Henrik Bruun[3], Pernille S. Kingo[4,5], Jørgen B. Jensen[4,5] and Sten Rasmussen[1]

[1]*Department of Clinical Medicine, Aalborg University,* [2]*Department of Urology,* [3]*Unit of Clinical Biostatistics, Aalborg University Hospital, Aalborg,* [4]*Department of Clinical Medicine, Aarhus University, and* [5]*Department of Urology, Aarhus University Hospital, Aarhus, Denmark*

Objective

To investigate the effectiveness and impact of low-pressure pneumoperitoneum (Pnp) on postoperative quality of recovery (QoR) and surgical workspace (SWS) in patients with prostate cancer undergoing robot-assisted radical prostatectomy (RARP).

Patients and Methods

A randomised, triple-blinded trial was conducted in a single centre in Denmark from March 2021 to January 2022. A total of 98 patients with prostate cancer undergoing RARP were randomly assigned to either low-pressure Pnp (7 mmHg) or standard-pressure Pnp (12 mmHg). Co-primary outcomes were postoperative QoR measured via the QoR-15 questionnaire on postoperative Day 1 (POD1), POD3, POD14, and POD30, and SWS assessed intraoperatively by a blinded assessor (surgeon) via a validated SWS scale. Data analysis was performed according to the intention-to-treat principle.

Results

Patients who underwent RARP at low Pnp pressure demonstrated better postoperative QoR on POD1 (mean difference = 10, 95% confidence interval [CI] 4.4–15.5), but no significant differences were observed in the SWS (mean difference = 0.25, 95% CI −0.02 to 0.54). Patients allocated to low-pressure Pnp experienced statistically higher blood loss than those in the standard-pressure Pnp group (mean difference = 67 mL, $P = 0.01$). Domain analysis revealed significant improvements in pain ($P = 0.001$), physical comfort ($P = 0.007$), and emotional state ($P = 0.006$) for patients with low-pressure Pnp. This trial was registered at ClinicalTrials.gov, NCT04755452, on 16/02/2021.

Conclusion

Performing RARP at low Pnp pressure is feasible without compromising the SWS and improves postoperative QoR, including pain, physical comfort, and emotional state, compared to the standard pressure.

Keywords

postoperative recovery, quality of recovery, QoR-15, surgical workspace, RARP, low pneumoperitoneum

Introduction

Robot-assisted radical prostatectomy (RARP) has become the 'gold standard' in surgery for localised prostate cancer.

Compared to classical open surgery, minimally invasive surgery (laparoscopic and robot-assisted surgeries) avoids large incisions and thus decreases blood loss, pain, discomfort, and admission time. Patients have fewer unwanted effects from analgesia because less analgesia is required [1,2].

Establishing pneumoperitoneum (Pnp) under surgery by insufflation of CO_2 into the peritoneal cavity starts a series of physiological changes in several vital organs. Increased intra-abdominal pressure (IAP), up to 12–14 mmHg, decreases venous return, cardiac preload, and cardiac output as well as increases heart rate [3,4]. Furthermore, CO_2 is readily absorbed, leading to hypercapnia and respiratory acidosis [5]. These physiological changes have no clinically significant effect on a healthy individual with an American Society of Anesthesiologists (ASA) score of I or II. However, for

comorbid patients with a higher ASA score of III–V, these changes may lead to serious, life-threatening complications [5]. Several clinical trials have reported adverse effects of high Pnp pressure on kidney, liver, and bowel functions [6–8].

Many different surgical procedures use a standard Pnp pressure of 12–15 mmHg [9]. However, international guidelines recommend using 'the lowest intra-abdominal pressure allowing adequate exposure of the operative field rather than a routine pressure' [10]. The possible reason that surgeons still prefer a standard-pressure Pnp is that they do not want to be challenged by a small workspace that may increase the risk of organ injury or limit the manoeuvrability of instruments.

We are not aware of any controlled trials that have addressed the effect of low-pressure Pnp on the quality of postoperative recovery and the surgical workspace (SWS) for patients undergoing RARP. In this study, we aimed to investigate how low IAP influences the quality of postoperative recovery and SWS during RARP.

Patients and Methods

Study Design and Participants

This study was a single-centre, randomised, triple-blinded superiority trial. Our aim was to compare the quality of postoperative recovery as measured by the quality of recovery-15 (QoR-15) questionnaire [11] and SWS as measured by the SWS scale [12] for low- (7 mmHg) vs standard-pressure (12 mmHg) Pnp during RARP. The treatment setting was at the Department of Urology, Aalborg University Hospital, Aalborg, Denmark. Eligible patients aged between 40 and 75 years with previously untreated, histologically confirmed, focal prostate cancer who were offered RARP. Patients were ineligible if they were not able to give informed consent, complete trial documentation, or speak or understand the Danish language.

The study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the North Denmark Region (N-20200078, 8 December 2020) and the Danish Data Protection Agency (2020-118, 28 September 2020). All patients provided written informed consent, and the trial proceeded according to Good Clinical Practice and Consolidated Standards of Reporting Trials (CONSORT) guidelines [13].

Randomisation and Masking

Research Electronic Data Capture (RedCap) software, hosted by Aalborg University Hospital, was used to collect data and conduct web-based randomisation. The patients were randomly assigned in a 1:1 ratio into a low- (7 mmHg) or a standard-pressure Pnp group (12 mmHg). The primary researcher organised the randomisation process and completed it while the patient was in the theatre. After the patient was anaesthetised, the sealed envelope containing the allocation group was handed over to the operating department practitioner (ODP) in the operating room. The surgeon was advised to set all surgical ports at a Pnp pressure of 10–12 mmHg. After the surgeon completed port placement and robot docking, the ODP opened the envelope and adjusted the Pnp pressure according to the assigned pressure group. The nurse covered the pressure indicator in the insufflator to ensure that the surgeon was unaware of the assigned pressure group and maintain the blinding measures. The patients were offered the option to be informed of the Pnp pressure after completing their postoperative Day 30 (POD30) final questionnaire. Two co-researchers (medical students) were trained to administer the questionnaire and were responsible for contacting the patients and completing the QoR-15 questionnaire. The co-researchers were also included in the blinding measures and remained uninformed of the patients' group allocations and randomisation.

Procedure

To reduce surgical heterogeneity and ensure minimal dropout from the intervention group, the procedures were performed by two high-volume surgeons, each of whom had carried out ≥300 RARPs prior to the trial.

At 1 day before the operation, the co-researchers contacted the patients and administered the QoR-15 questionnaire in collaboration with them.

All surgeries were conducted in a steep Trendelenburg position, as described by Huynh and Ahlering [14]. During the surgery, the surgeons used the SWS scale to assess SWS by assigning a score from 1 to 5 at three different points: (i) during bladder neck incision, (ii) during dissection of the seminal vesicle, and (iii) during dissection of the apex of the prostate. The dorsal venous complex (DVC) was controlled with a suture ligation technique in all cases and the Pnp pressure was not changed during the DVC dissection to ensure consistency in the procedure.

All patients received standard postoperative care, including early mobilisation, clear fluid intake, pain medication, and prophylactic anticoagulants. Patients were discharged home as soon as feasible, usually the following day. The co-researchers contacted the patients on POD1, POD3, POD14, and POD30 to complete the QoR-15 questionnaire.

Outcomes

The co-primary outcomes of this study were QoR as measured by the QoR-15 [11] and quality of the SWS as measured by the SWS scale [15]. The QoR-15 is a validated patient-reported outcome with a score ranging from 0 to 150 that assesses five domains of patient-reported status: pain, physical comfort, physical independence, psychological status,

and emotional status. A higher QoR-15 score indicates better recovery after surgery [16]. The SWS scale is a validated subjective scale used by surgeons to categorises the SWS from 1 to 5 points, with 1 meaning extremely poor conditions and 5 meaning optimal conditions.

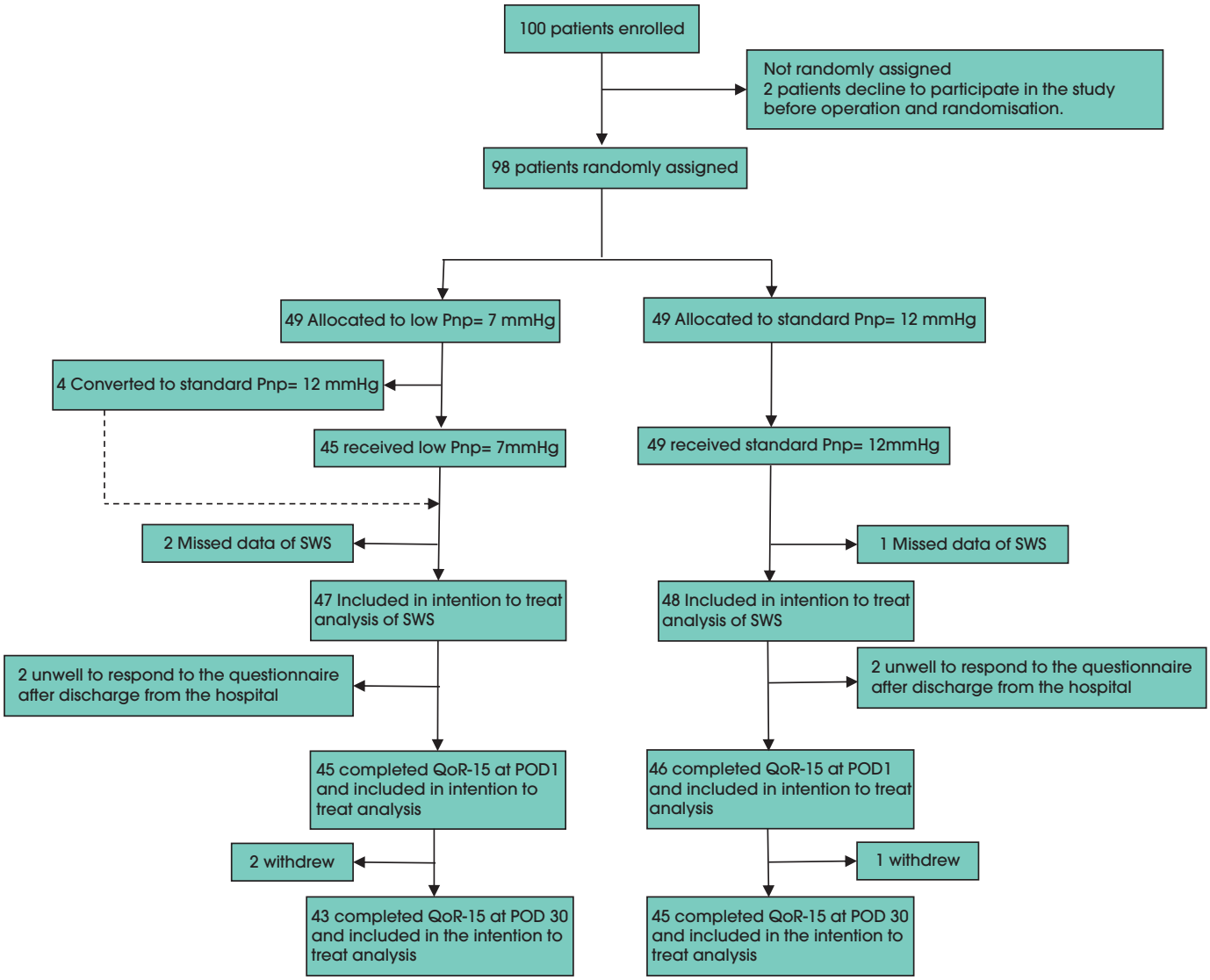
The secondary outcomes included blood loss during the procedure, operation time, length of hospital stay, complications within 90-days postoperatively (using the Clavien–Dindo classification) [17], and opioid use in the first 24 h as measured by morphine oral equivalent (MOE) [18].

Statistics

The sample size for this study was calculated to detect the mean of the minimal clinically important difference (MCID) between the treatment groups. The suggested MCID for the QoR-15 [11,19] was 10 points with an SD of 16, while the MCID for the SWS scale was 0.5 with an SD of 0.4 [20]. These MCIDs were based on the literature and discussions with specialists on relevant cut-offs. A total of 84 patients (42 in each group) were needed to detect the differences, which would provide 80% power to show a difference for QoR-15 and over 98% power for SWS scale at a two-sided alpha of 5%. To account for a 15% loss in follow-up, we recruited a total of 100 patients. All analyses were based on the intention-to-treat population. Mean, SD, and 95% CI or median and interquartile range (IQR) were reported for continuous data as appropriate, while categorical data were presented as *n* (%).

A repeated measures model using a robust variance estimate was used to estimate mean differences and 95% CIs for the

Fig. 1 Trial profile.



total score of the QoR-15 [21]. No imputation of missing data was performed.

Between-group differences were evaluated using the chi-square test for categorical variables and the *t*-test and non-parametric Mann–Whitney *U*-test for continuous variables. All analyses were conducted using STATA, version 17 (Stata Corp., College Station, TX, USA). This trial was registered with ClinicalTrials.gov, NCT04755452.

Role of Funding Source

There was no funding source for this study.

Results

From 2 March 2021 to 28 January 2022, we randomly assigned and allocated 98 patients (49 to the standard-pressure Pnp of 12 mmHg and 49 to a low-pressure Pnp of 7 mmHg). Four (8%) patients in the low-pressure Pnp group who required an increased Pnp pressure of 12 mmHg due to poor SWS or bleeding that hindered the surgeon's ability to complete the surgery were kept in the low-pressure Pnp group for analysis. Four patients, two (4%) from each group, withdrew from the study due to their unwillingness to complete the questionnaire after discharge from the hospital. The follow-up was completed in May 2022.

The final response rate for the QoR-15 questionnaire was 89%, with 43 (87%) of 49 patients in the low-pressure Pnp group and 45 (91%) of 49 patients in the standard-pressure Pnp group completing the last questionnaire at POD30 (Fig. 1).

The baseline patients' characteristics and demographics are described in Table 1.

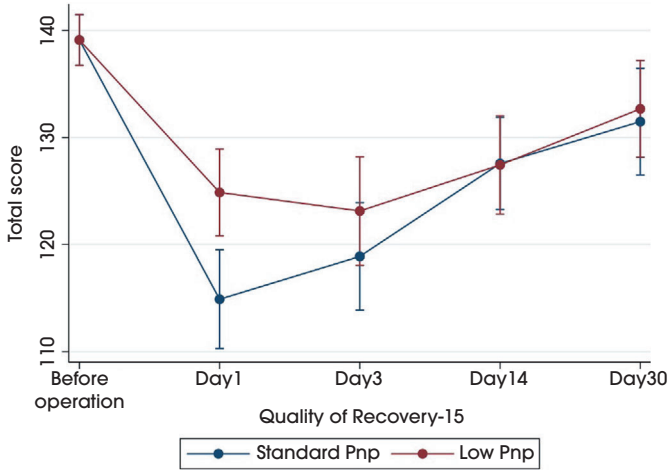
Patients allocated to the low-pressure Pnp group had a significantly better QoR, as measured by the QoR-15, on POD1 compared to those in the standard-pressure Pnp group, with scores of 124.8 (95% CI 120.8–128.9) vs 114.8 (95% CI 110.2–119.4; $P < 0.001$) and a between-group difference of 10 (95% CI 4.4–15.5). There were no significant differences between the groups on POD3, POD14, and POD30 (Fig. 2). Analysis of domains revealed a statistically significant improvement in pain, physical comfort, and emotional state in the low-pressure Pnp group on POD1 (Table 2). The standard-pressure Pnp group had a higher SWS scale score than the low-pressure Pnp group, but this difference was not statistically significant (4.2 [95% CI 4.0–4.4] vs 3.9 [95% CI 3.9–4.2]). The mean difference between groups was 0.25 (95% CI −0.02 to 0.54; $P = 0.07$). There were no differences in pathological outcomes, surgical margin status, total surgical time, length of hospital stay, or narcotic analgesics use during POD1. Patients allocated to the low-pressure Pnp group had significantly greater blood loss compared to the standard-pressure Pnp group (mean [SD] of 227 [147.3] vs 159.9 [110.4] mL; $P = 0.01$, Table 3). The incidence of postoperative complications was similar between the groups at 90 days of follow-up (Table S1).

Table 1 Baseline characteristics of the patients.

	Standard-pressure Pnp ($n = 49$)	Low-pressure Pnp ($n = 49$)
Age, years, mean (SD)	66.9 (6.3)	65.5 (7.0)
BMI, kg/m^2, mean (SD)	27.1 (2.8)	28.0 (3.5)
Hypertension, *n* (%)	19 (38.8)	22 (44.9)
Diabetes mellitus, *n* (%)	5 (10.2)	4 (8.2)
Previous abdominal surgery, *n* (%)	5 (10.2)	6 (12.2)
PSA level, ng/mL, mean (SD)	11.1 (7.5)	10.3 (6.7)
Prostate volume, mL, mean (SD)	54.3 (25.7)	51.8 (28.9)
T stage from DRE, *n* (%)		
T1c	24 (49.0)	28 (57.1)
T2a	9 (18.4)	11 (22.4)
T2b	12 (24.5)	6 (12.2)
T2c	4 (8.2)	4 (8.2)
ISUP Grade, *n* (%)		
2	16 (32.7)	19 (38.8)
3	16 (32.7)	12 (24.5)
4	3 (6.1)	4 (8.2)
5	14 (28.6)	14 (28.6)

Data presented as mean (SD) for continuous variables, and as n (%) for categorical variables. There is no baseline missing data. ISUP, International Society of Urological Pathology.

Fig. 2 Results of total QoR-15 between the low- and standard-pressure Pnp groups. Data presented as mean and 95% CI. The figure included only completed questionnaires with no imputation of missing data.



Discussion

This randomised controlled trial aimed to investigate the effect of low Pnp pressure on the postoperative QoR and

Table 2 The QoR-15 scores at POD1, POD3, POD14, and POD30.

	Standard-pressure Pnp, mean (95% CI)	Low-pressure Pnp, mean (95% CI)	Difference from standard-pressure Pnp, mean (95% CI)	*P*
QoR-15 total score				
POD1	114.8 (110.2–119.4)	124.8 (120.8–128.9)	10 (4.4–15.5)	<0.001
POD3	118.8 (113.8–123.9)	123.1 (118.0–128.1)	4.2 (−2.5–11.0)	0.22
POD14	127.5 (123.2–131.8)	127.4 (122.8–132.0)	−0.13 (−6.1–5.8)	0.96
POD30	131.4 (126.4–136.4)	132.6 (128.1–137.2)	1.1 (−5.2–7.6)	0.71
QoR-15 domains				
Pain				
POD1	13.7 (12.6–14.7)	16.0 (15.1–16.8)	2.3 (0.9–3.6)	0.001
POD3	15.5 (14.6–16.4)	15.7 (14.7–16.8)	0.21 (−1.1–1.6)	0.75
POD14	17.0 (16.1–17.9)	17.0 (16.0–18.1)	0.025 (−1.3–1.4)	0.97
POD30	17.8 (17.0–18.6)	18.3 (17.6–19.0)	0.49 (−0.5–1.5)	0.35
Physical comfort				
POD1	40.1 (38.3–41.8)	43.0 (41.6–44.4)	2.9 (0.8–5.1)	0.007
POD3	40.6 (38.6–42.7)	42.7 (40.9–44.5)	2.02 (−0.6–4.6)	0.13
POD14	43.7 (42.1–45.3)	43.5 (41.9–45.2)	−0.1 (−2.4–2.0)	0.88
POD30	45.0 (43.4–46.7)	44.9 (43.2–46.6)	−0.9 (−2.4–2.2)	0.93
Physical independence				
POD1	12.08 (11.1–13.0)	13.2 (12.2–14.3)	1.2 (−0.1–2.5)	0.08
POD3	13.7 (12.8–14.5)	13.3 (12–0-14.5)	−0.3 (−1.9–1.1)	0.61
POD14	15.4 (14.6–16.3)	15.1 (14.1–16.1)	−0.3 (−1.6–0.9)	0.62
POD30	16.3 (15.5–17.2)	16.5 (15.6–17.4)	0.1 (−1.0–1.3)	0.78
Psychological support				
POD1	19.3 (18.9–19.6)	19.6 (19.4–19.8)	0.3 (−0.5–0.7)	0.08
POD3	18.9 (18.5–19.4)	19.1 (18.6–19.7)	0.2 (−0.4–0.8)	0.53
POD14	19.1 (18.6–19.6)	19.3 (19.1–19.6)	0.2 (−0.3–0.7)	0.39
POD30	18.7 (18.0–19.4)	18.8 (18.0–19.5)	0.04 (−0.98–1.0)	0.93
Emotional state				
POD1	29.6 (27.6–31.6)	32.8 (31.0–34.7)	3.1 (0.9–5.4)	0.006
POD3	29.9 (27.9–31.9)	32.1 (30.4–33.9)	2.2 (−0.2–4.7)	0.07
POD14	32.1 (30.4–33.7)	32.1 (29.9–34.3)	0.0 (−2.5–2.6)	0.96
POD30	33.4 (31.5–35.3)	33.9 (32.0–35.9)	0.5 (−1.9–3.1)	0.67

Table 3 Secondary surgical outcomes.

	Standard-pressure Pnp (*n* = 49)	Low-pressure Pnp (*n* = 49)	*P*
Pathological outcomes			
Post-prostatectomy ISUP Grade, *n* (%)			
2	10 (20.4)	14 (28.6)	
3	31 (63.3)	25 (51.0)	
4	0 (0.0)	3 (6.1)	
5	8 (16.3)	7 (14.3)	0.22
Prostate volume after surgery, mL, mean (SD)	57.9 (21.6)	56.5 (29.1)	0.79
Positive surgical margin, *n* (%)	8 (16.3)	10 (20.4)	0.60
Post-prostatectomy stage, *n* (%)			
T2a	1 (2.0)	0 (0.0)	
T2b	2 (4.1)	2 (4.1)	
T2c	22 (44.9)	28 (57.1)	
T3a	21 (42.9)	16 (32.7)	
T3b	3 (6.1)	3 (6.1)	0.66
Perioperative outcomes			
Time of surgery, min, mean (SD)	152.1 (38.9)	156.1 (43.9)	0.64
Intraoperative bleeding, mL, mean (SD)	159.9 (110.4)	227.0 (147.3)	0.01
Narcotic analgesics (MOE) during the POD1, mg, median (IQR)	0 (0–25)	0 (0–15)	0.45
Length of hospital stay, days, mean (SD)	1.3 (0.7)	1.2 (0.5)	0.18
Postoperative blood transfusion, *n* (%)	0 (0)	0 (0)	

Data are mean (SD), n (%) or median (IQR). There is no missing data from secondary surgical outcomes.

SWS in patients undergoing RARP. To our knowledge, this is the first study to assess these outcomes using both patient- and surgeon-reported measures.

The results of this trial showed that low Pnp pressure significantly improved the postoperative QoR on the POD1, as measured by the QoR-15 questionnaire. There were no

significant differences in the mean SWS scale score between the low- and standard-pressure Pnp groups.

A recent meta-analysis identified four non-randomised studies investigating the effect of low- vs standard-pressure Pnp during RARP [22], but none of these included the QoR or assessment of SWS as primary or secondary outcomes.

Patients who underwent low-pressure Pnp RARP in our trial experienced significantly less pain and better physical comfort and emotional state on the POD1, according to sub-analysis of QoR-15 domains. Ferroni et al. [23] conducted a non-randomised prospective study comparing 15 vs 6 mmHg. Their results showed improvement in pain at 5–12 h in the low-pressure (6 mmHg) Pnp group but without significant differences in POD1. The research group later ran a randomised trial and reported a significant difference in immediate pain scores at 0–4 h [24]. Neither the two studies nor our data identified significant differences regarding narcotics administered during the first 24 h postoperatively. Our results regarding other secondary outcomes were comparable to results from the meta-analysis, which showed no significant difference in the total time of surgery, positive surgical margins, or Clavien–Dindo complications [22].

The results of our study showed that blood loss was statistically greater in the low-pressure Pnp group, with a mean difference of ~67 mL. While this difference was statistically significant, it was not clinically meaningful and had no significant impact on patient outcomes or the need for blood transfusion. This finding contradicts the results of the meta-analysis and the two randomised trials identified in our literature search, which demonstrated no significant difference in blood loss between the low- and standard-pressure Pnp groups [7,22,24].

There is conflicting data concerning the risk of postoperative ileus (POI). Three out of four non-randomised studies from the meta-analysis reported the risk of POI, with results indicating a significant decrease in the risk of POI under low Pnp pressure [22]. The two randomised trials found no significant difference in the rate of POI, but in one trial, patients in the low-pressure Pnp group reported passing flatus earlier [7,24]. Our results also demonstrated no significant difference in POI between the groups; only one patient in the control arm developed POI.

The major limitation of our study is that it is a single-institution trial in which only two high-volume surgeons performed the surgeries. As our results may not be directly generalisable to less experienced surgeons, this limitation could affect the generalisability of our findings, particularly when considering the potential risk of increased bleeding with less experienced surgeons.

Another limitation is the relatively low mean body mass index (BMI) in both groups. Our cohort included nine patients in the intervention arm with a BMI between 31 and 35 kg/m^2, while only three patients in the standard-pressure Pnp group have a BMI between 31 and 34 kg/m^2. Despite the presence of patients with a higher BMI, the completion of surgery in the low-pressure Pnp group was not adversely affected. However, we acknowledge the need for further studies to comprehensively evaluate the effects of low Pnp pressure in patients with a higher BMI.

The strengths of the study include triple-blinding of patients, surgeons, and observers, and the high response rate to the questionnaire, which added value to our results. Only four patients needed conversion from low- to standard-pressure Pnp. The authors of the QoR-15 questionnaire reported a new MCID of 6 points during the patient recruitment phase of our trial [25], which enhanced the power of our study's clinical difference and gives more solidity to our results.

Several animal studies have suggested that expanding the peritoneum may activate peritoneal inflammation and modulate the immune response, leading to hypoxia and acidosis in the peritoneum [26]. Other animal studies have found a significant linear correlation between Pnp pressure, free radical formation, and oxidative stress index [27,28]. Furthermore, many studies suggest that inflammatory factors, free radical formation, and oxidative stress may be involved in the recovery process after surgery [29,30]. Therefore, a low-pressure Pnp may decrease such unfavourable physiological changes and thereby improve the postoperative QoR.

Future research investigating the effect of low-pressure Pnp may include direct measurement of inflammatory parameters and free radicals.

Our results demonstrated that a low Pnp pressure is superior to the standard Pnp pressure in providing a better recovery during POD1 after RARP without sacrificing the SWS for the surgeon. Our trial results could be used to update the minimally invasive surgery guidelines and allow patients to benefit from low-pressure Pnp by avoiding the unwanted side-effects of high-pressure (standard) Pnp.

Author Contributions

Hayder Alhusseinawi contributed to the conception, literature search, study design, and data collection. Hayder Alhusseinawi and Niels Henrik Bruun contributed to the data analysis and interpretation. Sten Rasmussen, Lotte Sander designed and managed the qualitative analysis, project administration, supervision, review, and editing. Pernille M. Rosenvinge and Sarah L. Jensen contributed to data collection. Pernille S. Kingo and Jørgen B. Jensen contributed to the project design, review, and editing.

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Disclosure of Interests

Jørgen B. Jensen reports the following conflict of interest; Proctor: Intuitive Surgery, Member of Advisory Board: Ferring, Roche, Cepheid, Urotech, Olympus, AMBU, Speaker: Medac, Olympus, Intuitive Surgery, Photocure ASA, Research collaboration: Medac, Photocure ASA, Roche, Ferring, Karl Storz, Olympus, Intuitive Surgery, Astellas, Cepheid, Nucleix, Urotech, Pfizer, AstraZenica. All other authors declare no competing interests.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1 **Veldkamp R, Kuhry E, Hop WCJ et al.** Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. *Lancet Oncol* 2005; 6: 477–84

2 **Martínez-Pérez A, Carra MC, Brunetti F, de'Angelis N.** Short-term clinical outcomes of laparoscopic vs open rectal excision for rectal cancer: a systematic review and metaanalysis. *World J Gastroenterol* 2017; 23: 7906–16

3 **Stuttmann R, Vogt C, Eypasch E, Doehn M.** Haemodynamic changes during laparoscopic cholecystectomy in the high-risk patient. *Endosc Surg Allied Technol* 1995; 3: 174–9

4 **Dexter SP, Vucevic M, Gibson J et al.** Hemodynamic consequences of high- and low-pressure capnoperitoneum during laparoscopic cholecystectomy. *Surg Endosc* 1999; 13: 376–81

5 **Neudecker J, Sauerland S, Neugebauer E et al.** The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. *Surg Endosc Other Interv Tech* 2002; 16: 1121–43

6 **Demyttenaere S, Feldman LS, Fried GM.** Effect of pneumoperitoneum on renal perfusion and function: a systematic review. *Surg Endosc Other Interv Tech* 2007; 21: 152–60

7 **Rohloff M, Peifer G, Shakuri-Rad J, Maatman TJ.** The impact of low pressure pneumoperitoneum in robotic assisted radical prostatectomy: a prospective, randomized, double blinded trial. *World J Urol* 2020; 39: 3–8

8 **Nguyen NT, Braley S, Fleming NW, Lambourne L, Rivers R, Wolfe BM.** Comparison of postoperative hepatic function after laparoscopic versus open gastric bypass. *Am J Surg* 2003; 186: 40–4

9 **Hypólito OHM, Azevedo JLMC, De Lima Alvarenga Caldeira FMS et al.** Creation of pneumoperitoneum: Noninvasive monitoring of clinical effects of elevated intraperitoneal pressure for the insertion of the first trocar. *Surg Endosc* 2010; 24: 1663–9

10 EAES guidelines for endoscopic surgery. 2006. Epub ahead of print 2006 https://doi.org/10.1007/978-3-540-32784-4

11 **Stark PA, Myles PS, Burke JA.** Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013; 118: 1332–40

12 **Alhusseinawi H, Haase R, Rasmussen S, Jensen JB, Kingo PS.** Validation of a surgical workspace scale during robot-assisted surgery. *Int J Med Robot Comput Assist Surg* 2023; 19: 5–8

13 **Moher D, Hopewell S, Schulz KF et al.** CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012; 10: 28–55

14 **Huynh LM, Ahlering TE.** Robot-assisted radical prostatectomy: a step-by-step guide. *J Endourol* 2018; 32: S28–32

15 **Alhusseinawi H, Haase R, Rasmussen S, Jensen JB, Kingo PS.** Validation of a surgical workspace scale during robot-assisted surgery. *Int J Med Robot* 2022; 19: e2482

16 **Kleif J, Edwards HM, Sort R, Vilandt J, Gögenur I.** Translation and validation of the Danish version of the postoperative quality of recovery score QoR-15. *Acta Anaesthesiol Scand* 2015; 59: 912–20

17 **Dindo D, Demartines N, Clavien PA.** Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205–13

18 **Nielsen S, Degenhardt L, Hoban B, Gisev N.** A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf* 2016; 25: 733–7

19 **Ivry M, David G, Wiam W et al.** Melatonin premedication improves quality of recovery following bariatric surgery – a double blind placebo controlled prospective study. *Surg Obes Relat Dis* 2017; 13: 502–6

20 **Torensma B, Martini CH, Boon M et al.** Deep neuromuscular block improves surgical conditions during bariatric surgery and reduces postoperative pain: a randomized double blind controlled trial. *PLoS One* 2016; 11: 1–14

21 **Twisk J, Bosman L, Hoekstra T, Rijnhart J, Welten M, Heymans M.** Different ways to estimate treatment effects in randomised controlled trials. *Contemp Clin Trials Commun* 2018; 10: 80–5

22 **El-Taji O, Howell-Etienne J, Taktak S et al.** Lower vs standard pressure pneumoperitoneum in robotic-assisted radical prostatectomy: a systematic review and meta-analysis. *J Robot Surg* 2022; 17: 303–12

23 **Ferroni MC, Abaza R.** Feasibility of robot-assisted prostatectomy performed at ultra-low pneumoperitoneum pressure of 6 mmHg and comparison of clinical outcomes vs standard pressure of 15 mmHg. *BJU Int* 2019; 124: 308–13

24 **Abaza R, Ferroni MC.** Randomized trial of ultralow vs standard pneumoperitoneum during robotic prostatectomy. *J Urol* 2022; 208: 626–32

25 **Myles PS, Myles DB.** An updated minimal clinically important difference for the QoR-15 scale. *Anesthesiology* 2021; 135: 934–5

26 **Brokelman WJA, Lensvelt M, Rinkes IHMB, Klinkenbijl JHG, Reijnen MMPJ.** Peritoneal changes due to laparoscopic surgery. *Surg Endosc* 2011; 25: 1–9

27 **Lee JY, Choi SH.** Evaluation of total oxidant and antioxidant status in dogs under different CO_2 pneumoperitoneum conditions. *Acta Vet Scand* 2015; 57: 1–6

28 **Sare M, Yilmaz I, Hamamci D, Birincioglu M, Özmen M, Yesilada Ö.** The effect of carbon dioxide pneumoperitoneum on free radicals. *Surg Endosc* 2000; 14: 649–52

29 **McSorley ST, Watt DG, Horgan PG et al.** Postoperative systemic inflammatory response, complication severity, and survival following surgery for colorectal cancer. *Ann Surg Oncol* 2016; 23: 2832–40

30 **Tsuchiya M, Shiomoto K, Mizutani K et al.** Reduction of oxidative stress a key for enhanced postoperative recovery with fewer complications in esophageal surgery patients randomized control trial to investigate therapeutic impact of anesthesia management and usefulness of simple blood test for pre. *Medicine* 2018; 97: e12845

Correspondence: Hayder Alhusseinawi, Department of Clinical Medicine, Aalborg University, Selma lagerløfs vej 249 9260 Gistrup, Denmark.

e-mail: alhusseinawi.h@gmail.com

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; DVC, dorsal venous complex; IAP, intra-abdominal pressure; IQR, interquartile range; ISUP, International Society of Urological Pathology; MCID, minimal clinically important difference; MOE, morphine oral equivalent; ODP, operating department practitioner; Pnp, pneumoperitoneum; POD, postoperative day; POI, postoperative ileus; QoR(-15), quality of recovery(-15); RARP, robot-assisted radical prostatectomy; RedCap, Research Electronic Data Capture; SWS, surgical workspace.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Postoperative surgical complication at 3 months (Clavien–Dindo score).

Appendix C. Paper 3 (Submitted)

Impact of Low Pneumoperitoneum on Renal Function and Acute Kidney Injury Biomarkers during Robot-Assisted Radical Prostatectomy (RARP): A Randomised Clinical Trial

Hayder Alhusseinawi[1,2]; Lotte Sander [2]; Aase Handberg [1,3]; Rikke W. Rasmussen [3]; Pernille S. Kingo[4,5]; Jørgen B. Jensen[4,5]; Sten Rasmussen[1]

[1]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

[2]Department of Urology, Aalborg university hospital, Aalborg, Denmark

[3]Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark.

[4]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[5]Department of Urology, Aarhus university hospital, Aarhus, Denmark

Correspondent Author:

Hayder Alhusseinawi

E-mail: Alhusseinawi.h@gmail.com

Telephone number: +4542639615

Orchid No.: 0000-0002-2170-3771

Keywords: Low pneumoperitoneum, u-NGAL, Postoperative AKI, Renal injury Biomarkers.

Abstract

The objective of this study was to evaluate the effect of low pneumoperitoneum pressure (Pnp) on renal function and renal injury biomarkers during robot-assisted radical prostatectomy (RARP). A single-centre, triple-blinded, randomised clinical trial was conducted with 98 patients undergoing RARP, who were assigned to either standard Pnp of 12 mmHg or low Pnp of 7 mmHg. The primary outcome was urinary neutrophil gelatinase-associated lipocalin (u-NGAL), and several other kidney injury biomarkers were assessed as secondary outcomes. Acute kidney injury (AKI) was evaluated using the Kidney Disease Improving Global Outcomes (KDIGO) criteria, the gold standard method for defining AKI. The trial was registered on ClinicalTrials.gov (NCT04755452). Patients in the low Pnp group had significantly lower levels of u-NGAL (mean difference -39.9, 95% CI -73.7 to -6.1, p=0.02) compared to the standard Pnp group. No significant differences were observed for other urinary biomarkers. Interestingly, there was a significant difference in intraoperative urine production between the groups (low Pnp median: 200 mL, IQR: 100-325 vs. standard Pnp median: 100 mL, IQR: 50-200, p=0.01). Similarly, total postoperative urine production also varied significantly (low Pnp median: 1325 mL, IQR: 1025-1800 vs. standard Pnp median: 1000 mL, IQR: 850-1287, p=0.001). The occurrence of AKI, as defined by the KDIGO criteria, did not differ significantly between the groups. Low Pnp during RARP resulted in lower u-NGAL levels, suggesting a potential benefit in terms of reduced renal injury. However, the lack of a notable difference in AKI as defined by the KDIGO criteria indicates that the clinical significance of this finding may be limited. Further research is needed to validate and expand on these results, ultimately defining the optimal Pnp strategy for RARP and improving patient outcomes.

Introduction

The effect of pneumoperitoneum (Pnp) on kidney physiology has become an area of investigation, particularly as laparoscopic and robot-assisted surgical procedures continue to gain prominence. Robot-assisted radical prostatectomy (RARP) has become the gold standard in surgery for localised prostate cancer. Compared to open radical prostatectomy, RARP has a higher risk of developing transient Acute kidney injury (AKI). [1]

The incidence of AKI after RARP contributes primarily to the Pnp that is believed to be associated with renal changes. The mechanism behind this is not well understood. But it is likely to be caused by direct compression of Pnp on renal parenchyma and vasculature, leading to increased vascular resistance, venous and lymphatic congestion, and decreased renal blood flow. [2, 3] Renal autoregulation results in the stimulation of the renin–angiotensin–aldosterone system (RAAS), with increasing renin release and subsequent aldosterone secretion. Secondly, neuroendocrine responses result in the excretion of the anti-diuretic hormone. This results in salt and water retention with oliguria and a vicious cycle of renal cortical vasoconstriction leading to further activation of the RAAS.[4]

These changes results in reduced renal blood flow and glomerular filtration rate, which can have implications for patient outcomes. As such, understanding the impact of pneumoperitoneum pressure on various biomarkers associated with kidney function is crucial in augmenting surgical techniques and minimising potential adverse effects on renal function.

In recent years, several kidney biomarkers have been identified as useful indicators of renal function and potential predictors of kidney injury. These biomarkers include Neutrophil Gelatinase-Associated Lipocalin (NGAL), Vascular Endothelial Growth Factor (VEGF), Osteoactivin, Kidney Injury Molecule-1 (KIM-1), Trefoil factor 3 (TFF3), Clusterin, and Calbindin. Each of these biomarkers plays a distinct role in kidney physiology and is expressed in the specific tubular or interstitial component of the kidney.[5]

Urinary NGAL is a protein rapidly upregulated in response to kidney injury, serving as an early and sensitive marker for acute kidney injury (AKI). It has been shown to predict the severity of renal dysfunction.[6–8]

Given the importance of these biomarkers in assessing renal function and injury, understanding how different pneumoperitoneum pressures impact their levels during RARP is vital. This study aimed to investigate the effect of low Pnp on renal function urinary biomarkers through a randomised clinical trial. The results are expected to offer valuable insights into the potential impact of pneumoperitoneum on renal function and inform surgical practice, thereby minimising adverse renal effects during laparoscopic procedures.

To our knowledge, this is the first study investigating the effect of pneumoperitoneum on urinary kidney injury markers.

Methods

2. Materials and methods

2.1. Study design and participants

This study was a single-centre, triple-blinded, randomised clinical trial. We aimed to investigate the effect of low Pnp on renal function for patients with prostate cancer who underwent robot-assisted radical prostatectomy (RARP) at the Department of Urology, Aalborg University Hospital, Aalborg, Denmark. Eligible patients aged between 40 and 75 years old with previously untreated, histologically confirmed, focal prostate cancer who were offered RARP. Patients were ineligible if they were not able to give informed consent, complete trial documentation, or speak or understand the Danish language.

The study complied with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the North Denmark Region (N-20200078, 08. December 2020) and the Danish Data Protection Agency (2020-118, 28. September 2020), and registered at ClinicalTrials.gov (NCT04755452, 16. February 2021) All patients provided written informed consent, and the trial proceeded according to Good Clinical Practice and CONSORT guidelines.[9]

We used RedCap (Research Electronic Data Capture) software provided by Aalborg University Hospital to collect data and perform web-based randomisation.

2.2. Procedure

To reduce surgical heterogeneity and ensure minimal dropout from the intervention group, the procedures were performed by two high-volume surgeons, each of whom had carried out at least 300 RARPs prior to the trial. All surgeries were conducted in the steep Trendelenburg position, and as described by Huynh et al.[10] After

administering general anaesthesia, the operating department practitioner (ODP) inserted a urinary catheter before starting the surgery. They collected 20 mL of urine and documented intraoperative urine production. The dorsal venous complex (DVC) was handled using a suture ligation method, and to maintain consistency throughout the procedure, the pneumoperitoneum pressure (Pnp) was kept constant during DVC dissection.

Nurses in the ward recorded urine production postoperatively. On the next day, as the patient prepared for discharge, they collected another 20 mL of urine before the patient left the ward. The samples were stored at -80°C for future analysis of urinary kidney injury markers. Blood tests for serum creatinine were conducted one week before surgery, on the 1st postoperative day (POD), and lastly, at 10^{th} POD.

2.3. Randomisation and masking

RedCap (Research Electronic Data Capture) software, hosted by Aalborg University Hospital, was used to collect data and conduct web-based randomisation. The patients were randomly assigned in a 1:1 ratio into a low Pnp (7 mmHg) or a standard Pnp group (12 mmHg). The primary researcher organised the randomisation process and completed it while the patient was in the theatre. After the patient was anaesthetised, the sealed envelope containing the allocation group was handed over to the ODP in the operating room. The surgeon was advised to set all surgical ports at Pnp = 10–12 mmHg. After the surgeon completed port placement and robot docking, the ODP opened the envelope and adjusted the Pnp according to the assigned pressure group. The nurse covered the pressure indicator in the insufflator to ensure that the surgeon was unaware of the assigned pressure group and maintain the blinding measures. Medical Laboratory technologists were also included in the blinding measures and remained uninformed of the patients' group allocations and randomisation.

2.4. Outcomes

The primary outcome is the change in urinary Neutrophil Gelatinase-Associated Lipocalin (u-NGAL) before and after surgery. Secondary outcomes include changes in urinary markers that represent all nephron segments, urinary electrolytes, creatinine and albumin. We also assessed the risk of AKI according to the standard; Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[11]

2.5. Analysis of urine samples

The Human Lipocalin-2/NGAL Quantikine ELISA Kit from RnD (Biotechne, UK, Cat # DLCN20, lot # P306758) was used to determine u-NGAL as described by the manufacturer. . Samples were analysed in singlets, diluted 5-20 fold. Controls were included at each run. Inter-assay coefficients of variation (CVs) in 7 runs were 6.1 % (level 0.9 ng/mL), 3.5 % (level 2.8 ng/mL) and 5.4 % (level 5.5 ng/mL). Pre- and post-surgery samples were analysed on the same plate.

The kidney injury markers Calbindin, Clusterin, KIM-1, Osteoactivin, TFF3 and VEGF were analysed by the ELISA multiplex assay (Kidney Injury Panel 3 (human) Kit Cat# K15189D-1 Lot# K0040523, Meso Scale Discovery (MSD), Rockville, USA) according to the manufacturer's protocol. In short, the 96-well precoated plates were incubated with blocking buffer and washed 3 times with premade wash buffer: PBS (Lonza Cat#17-512-F), 0.05% Tween-20 (Sigma P9416-100ml) at an ELx50 BioTek plate was before analysis. Urine samples were thawed, mixed, and subjected to a quick spin at 17000g and diluted 1:10 in 96 well dilution plates in singlets, together with standards and KIM-1 controls (R&D systems, cat# C24, Lot# P292291) in duplicate. Fifty µl of samples, standards and controls were transferred to the MSD plate and incubated for 2 hours, washed, and incubated with detection antibody for 2 hours. Subsequently, the plate was washed, and read buffer was added. The plates

were immediately read at a MESO QuickPlex SQ120MM Reader. Pre- and post-surgery samples were analysed on the same plate.

For analysis of the results, we used MSD Discovery Workbench version 4.0. Standard curves were generated from serially diluted calibrator by 4-parameter logistic regression. Nine samples obtained values either above or below the detection range for KIM-1, Clusterin, VEGF and/or Calbindin and were repeated in appropriate dilutions or undiluted. Out of 177 results, 103 were below the detection limit for TFF3 in dilution 1:10, and on this background, results for TFF3 are not reported. KIM-1 control results were used for the calculation of intra- and inter-assay CV. Mean intra-assay CV was 5.1% (level 4834.9 pg/ml, N=3 duplicates) and 3.3% (level 1548.5 pg/ml, N=3 duplicates), and inter-assay CV's were 14.3% and 10.8%, respectively (N=3 plates). The concentrations of potassium, sodium, chloride, creatinine, and albumin in urine were measured on a Cobas 6000 (Roche, Germany)at the Clinical Biochemistry Department..

2.6. Statistics

All analyses were based on the intention-to-treat population. Mean, standard deviation (SD) and 95% confidence interval (CI) or median and interquartile range (IQR) were reported for continuous data as appropriate, while categorical data were presented as n (%).

A repeated measures model using a robust variance estimate was used to estimate mean differences and 95% confidence intervals for the urinary kidney injury biomarkers.[12] No imputation of missing data was performed.

Between-group differences were evaluated using the Chi-square or Fisher exact tests for categorical variables and the t-test and nonparametric Mann-Whitney U test for continuous variables. All analyses were conducted using STATA (version 17).

3. Results

Between 2nd March 2021 and 28th January 2022, 98 patients were randomly assigned and allocated to either a standard Pnp of 12 mmHg (n=49) or a low Pnp of 7 mmHg (n=49) during robot-assisted radical prostatectomy (RARP). However, four patients (8%) from the low Pnp group necessitated an elevation of Pnp to 12 mmHg for longer than 20 minutes due to inadequate workspace or bleeding. Despite this adjustment, these patients were maintained in the low Pnp group as per the intention-to-treat principle for subsequent analysis., trial profile (Figure1).

Baseline patient characteristics and demographics are described in Table 1.

Postoperatively, patients in the low Pnp group demonstrated significantly lower levels of NGAL compared to the standard Pnp group (mean difference -39.9, 95% CI -73.7 to -6.1, p=0.02). No significant differences were observed for other urinary biomarkers (Table 2), nor for urinary electrolyte and Albumin Creatinine Ratio (ACR) (Table 3).

A significant difference was found in intraoperative urine production (median [IQR]: 100 [50-200] for standard Pnp vs 200 [100-325] for low Pnp, p=0.01) and total postoperative urine production (median [IQR]: 1000 [850-1287] for standard Pnp vs 1325 [1025-1800] for low Pnp, p=0.001). No significant differences were observed for other renal function parameters (Table 4).

The occurrence of AKI, defined according to the KDIGO criteria, was compared between patients. On the first day, AKI stage 1 was observed in 16 (32.6%) patients with low Pnp and 18 (36.7%) patients with standard Pnp, with no significant difference between the groups (p=0.67). For AKI stage 2 on the first day, fewer patients developed this stage in the low Pnp group, with 2 (4%) patients compared to 5 (10%) patients in the standard Pnp group. However, this difference was not statistically significant (p=0.43). By the 10th day post-operation, 6 (12%) patients in each group still had a symptomatic stage 1 AKI, with no significant difference between the groups (p=1.0).According to the cutoff of u-NGAL reported in previous studies that can predict AKI stage 2/3 as 78ng/ml,[13] our results showed that 3 (7%) from low Pnp and 5 (11%) from standard Pnp developed AKI stage 2/3 (p=0.73).

4. Discussion

To the best of our knowledge, this study is the first to investigate the effect of low Pnp on renal function utilising a spectrum of urinary biomarkers.

We observed a stable level of u-NGAL in the low Pnp group after surgery, which may be interpreted as minimal renal changes or milder effects within this group. In contrast, the standard Pnp group demonstrated an increase in u-NGAL levels, indicating a higher degree of renal impact. However, even this elevated level did not exceed the clinical threshold of 78 ng/ml, a previously identified cut-off value predictive of AKI.[13] Therefore, while the increase was statistically significant, it may not suggest a clinically meaningful difference.

The significant decrease in intra- and postoperative urine production in the standard Pnp group may have contributed to this mildly elevated u-NGAL.

In a somewhat contrasting observation, Filho et al.'s study examining the effect of low Pnp during laparoscopic cholecystectomy, no significant difference in plasma NGAL was observed 24 hours post-surgery between the standard (10-12 mmHg) and low Pnp (6-8 mmHg) groups.[14] This contrast with our findings could potentially be explained by the duration of surgery and the consequent exposure to Pnp. Filho et al. reported a duration of 70 minutes for the standard Pnp group and 77 minutes for the low Pnp group during laparoscopic cholecystectomy. In contrast, our more intricate procedure, radical prostatectomy, had a longer Pnp duration: 152 minutes for the standard Pnp group and 156 minutes for the low Pnp group.

These divergent findings are also corroborated by animal studies showing a strong correlation between increased NGAL levels and the duration of Pnp exposure. Notably, one study on rats documented significant increases in NGAL levels after the second hour of exposure to Pnp, a pattern consistent with our observations.[15] The study also showed that this increase was more pronounced at high Pnp. While serum creatinine levels remained unchanged, novel markers like NGAL presented a clear response to prolonged Pnp, underscoring their sensitivity in detecting renal injury.

The AKI detection using u-NGAL was well aligned with the KDIGO criteria in defining stage 2/3 AKI. Caution is necessary when interpreting these findings, as the lack of a notable difference in the gold standard definition of AKI by KDIGO between the two groups suggest that the observed variation in u-NGAL levels might not have a considerable influence on overall renal function or clinical outcomes. There are no changes in other kidney injury markers identified.

The renal epithelial biomarkers Calbindin, Clusterin, KIM-1, Osteoactivin (OA), and VEGF are known to indicate kidney damage and display elevated levels in urine across various kidney disorders.[16, 17] Calbindin is an extracellular Ca^{2+} binding protein that is primarily expressed by distal tubular and collecting duct cells. [18, 19] It is linked to distal tubular cell damage, and exhibits increased expression in vitro following exposure to agents like cisplatin [20]. Studies showed a strong correlation between urinary calbindin levels and AKI. [17, 21] OA, also known as glycoprotein

non-melanoma clone B (gpnmb), is a protein that plays a crucial role in the differentiation and functioning of various cell types. The therapeutic potential of OA has been explored in tissue regeneration for bone defects, liver damage, muscle atrophy, and kidney injury. [22] High expression of OA in the tubular epithelial cells and renal interstitium was identified in the animal model after unilateral ureteral obstruction.[23]

In cases of acute kidney injury (AKI) resulting from intrinsic renal causes, significant proximal tubular injury can occur. This tubular injury may hinder the proximal tubule's ability to reabsorb albumin, leading to albuminuria.[24] Prior research has demonstrated that the urinary Albumin-Creatinine Ratio (u-ACR) serves as a sensitive biomarker for detecting AKI, and it can predict the risk of AKI earlier than serum creatinine levels alone.[25, 26]

Considering the current findings, the clinical implications of using low Pnp during RARP merit further exploration. The reduced u-NGAL levels observed in the low Pnp group may suggest a potential role for low Pnp in minimising renal injury and promoting faster recovery. The lack of a notable difference in the gold standard definition of AKI by KDIGO between the two groups suggests that the clinical impact may be limited. It is valuable to investigate if specific patient populations, such as those with pre-existing renal conditions or during more complex and lengthy procedures such as radical cystectomy, will benefit more from low Pnp.

Our study has several limitations. The single-centre design may limit the generalisability of the results, and future multicenter studies with larger sample sizes may provide more robust evidence. Additionally, the short follow-up period may not be sufficient to detect any long-term effects of low Pnp on renal function.

Future research needs to focus on addressing these limitations and further investigate the effect of low Pnp on renal function during RARP. Long-term follow-up studies may reveal more pronounced differences in renal function between the two Pnp groups.

In conclusion, this study demonstrated low Pnp during RARP resulted in lower u-NGAL levels, suggesting a potential benefit in terms of reduced renal injury. However, the lack of a difference in AKI as defined by the KDIGO criteria between the groups indicates that the clinical significance of this finding may be limited. Further research is needed to validate and expand on these results, ultimately informing the optimal Pnp strategy for RARP and improving patient outcomes.

Statements and Declarations:

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

HA contributed to the conception, literature search, study design, data collection, data analysis, and interpretation. AH and RR were responsible for the biochemical analysis. SR and LS designed and managed qualitative analysis, project administration, supervision and participated in the review and editing process. PSK, JBJ, and AH contributed to the project design and provided their expertise in the review and editing stages.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the North Denmark Region (N-20200078, 08. December 2020) and the Danish Data Protection Agency (2020-118, 28. September 2020), and registered at ClinicalTrials.gov (NCT04755452, 16. February 2021).

Consent to participate.

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and material: Data is available upon reasonable request.

References:

[1] Naito A, Taguchi S, Suzuki M, et al. Transient acute kidney injury observed immediately after robot-assisted radical prostatectomy but not after open radical prostatectomy. *Mol Clin Oncol* 2020; 13: 1–5.

[2] Vasdev N, Sau A, Poon K, et al. The Physiologic and Anesthetic Considerations in Elderly Patients Undergoing Robotic Renal Surgery. *Rev Urol* 2014; 16: 1–9.

[3] Kopitkó C, Rosivall L, Medve L, et al. Pneumoperitoneum and Acute Kidney Injury - An Integrative Clinical Concept Review. *ASAIO J* 2023; 69: E54–E65.

[4] Sodha S, Nazarian S, Adshead JM, et al. Effect of pneumoperitoneum on renal function and physiology in patients undergoing robotic renal surgery. *Current Urology* 2015; 9: 1–4.

[5] Thangaraj SS, Thiesson HC, Svenningsen P, et al. Mineralocorticoid receptor blockade with spironolactone has no direct effect on plasma IL-17A and injury markers in urine from kidney transplant patients. *Am J Physiol - Ren Physiol* 2022; 322: F138–F149.

[6] Bennett M, Dent CL, Ma Q, et al. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol* 2008; 3: 665–673.

[7] Shang W, Wang Z. The Update of NGAL in Acute Kidney Injury. *Curr Protein Pept Sci* 2017; 18: 1211–1217.

[8] Schinstock CA, Semret MH, Wagner SJ, et al. Urinalysis is more specific and urinary neutrophil gelatinase-associated lipocalin is more sensitive for early detection of acute kidney injury. *Nephrol Dial Transplant* 2013; 28: 1175–1185.

[9] Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *Int J Surg* 2012; 10: 28–55.

[10] Huynh LM, Ahlering TE. Robot-Assisted Radical Prostatectomy: A Step-by-Step Guide. *J Endourol* 2018; 32: S28–S32.

[11] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clin Pract* 2012; 120: c179-84.

[12] J T, L B, T H, et al. Different ways to estimate treatment effects in randomised controlled trials. *Contemp Clin Trials Commun* 2018; 10: 80–85.

[13] Tecson KM, Erhardtsen E, Eriksen PM, et al. Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: Retrospective determination and

clinical validation of a prospective multicentre study. *BMJ Open* 2017; 7: 1–8.

[14] Marton Filho MA, Alves RL, Nascimento P do J, et al. Effects of pneumoperitoneum on kidney injury biomarkers: A randomized clinical trial. *PLoS One* 2021; 16: e0247088.

[15] Kozan R, Şare M, Yılmaz TU, et al. Effectiveness of new parameters in the evaluation of pneumoperitoneum-related acute kidney injury in rats. *Turkish J Med Sci* 2018; 48: 1278–1284.

[16] Brott DA, Adler SH, Arani R, et al. Characterization of renal biomarkers for use in clinical trials: biomarker evaluation in healthy volunteers. *Drug Des Devel Ther* 2014; 8: 227–237.

[17] Won AJ, Kim S, Kim YG, et al. Discovery of urinary metabolomic biomarkers for early detection of acute kidney injury. *Mol Biosyst* 2016; 12: 133–144.

[18] Iida T, Fujinaka H, Xu B, et al. Decreased urinary calbindin 1 levels in proteinuric rats and humans with distal nephron segment injuries. *Clin Exp Nephrol* 2014; 18: 432–443.

[19] Hemmingsen C. Regulation of renal calbindin-D28K. *Pharmacol Toxicol* 2000; 87 Suppl 3: 5–30.

[20] Takashi M, Zhu Y, Miyake K, et al. Urinary 28-kD calbindin-D as a new marker for damage to distal renal tubules caused by cisplatin-based chemotherapy. *Urol Int* 1996; 56: 174–179.

[21] Lane BR, Babitz SK, Vlasakova K, et al. Evaluation of Urinary Renal Biomarkers for Early Prediction of Acute Kidney Injury Following Partial Nephrectomy: A Feasibility Study. *Eur Urol Focus* 2020; 6: 1240–1247.

[22] Huang Y, Bai B, Yao Y. Prospects of osteoactivin in tissue regeneration. *Expert Opin Ther Targets* 2016; 20: 1357–1364.

[23] Nakamura A, Ishii A, Ohata C, et al. Early induction of osteoactivin expression in rat renal tubular epithelial cells after unilateral ureteral obstruction. *Exp Toxicol Pathol Off J Gesellschaft fur Toxikologische Pathol* 2007; 59: 53–59.

[24] Bolisetty S, Agarwal A. Urine albumin as a biomarker in acute kidney injury. *Am J Physiol - Ren Physiol* 2011; 300: 626–627.

[25] Zappitelli M, Coca SG, Garg AX, et al. The association of albumin/creatinine ratio with postoperative AKI in children undergoing cardiac surgery. *Clin J Am Soc Nephrol* 2012; 7: 1761–1769.

[26] Schnabel K, Garam N, Ledó N, et al. Urinary albumin-to-creatinine ratio and serum albumin are predictors of acute kidney injury in non-ventilated COVID-19 patients: a single-center prospective cohort study. *Int Urol Nephrol* 2023; 55: 711–720.

	Standard Pnp (n=49)	**Low Pnp (n=49)**
Age, year	66.9 (6.3)	65.5 (7.0)
BMI	27.1 (2.8)	28.0 (3.5)
Hypertension	19 (38.8%)	22 (44.9%)
DM	5 (10.2%)	4 (8.2%)
Previous abdominal surgery	5 (10.2%)	6 (12.2%)
PSA	11.1 (7.5)	10.3 (6.7)
Prostate volume, ml	54.3 (25.7)	51.8 (28.9)
T stage from DRE		
T1c	24 (49.0%)	28 (57.1%)
T2a	9 (18.4%)	11 (22.4%)
T2b	12 (24.5%)	6 (12.2%)
T2c	4 (8.2%)	4 (8.2%)
ISUP grade		
2	16 (32.7%)	19 (38.8%)
3	16 (32.7%)	12 (24.5%)
4	3 (6.1%)	4 (8.2%)
5	14 (28.6%)	14 (28.6%)

Data presented as mean (SD) for continuous variables, and as n (%) for categorical variables. There is no baseline missing data. PSA=prostate specific antigen.DRE= digital rectal examination. ISUP grade: International Society of Urologic Pathologists.

***Table 1*: Baseline characteristics of patients**

		After surgery: mean	sd	Before surgery: mean	sd	Effect: Diff from 12mm Hg	[95%	CI]	p-value
NGAL (ng/ml)	12 mmHg	60.9	109.5	22.5	35.2				
	7 mmHg	22.8	21.5	22.5	35.2	-39.9	-73.7	-6.1	0.02
VEGF (pg/ml)	12 mmHg	1109.9	1837.5	2393.5	5115.1				
	7 mmHg	617.5	536.6	2393.5	5115.1	-492.4	-1067.5	82.7	0.09
Osteoactivin (pg/ml)	12 mmHg	10294.9	9770.4	3011.8	2515.5				
	7 mmHg	7160.0	5030.4	3011.8	2515.5	-3105.4	-6394.3	183.6	0.06
KIM-1 (pg/ml)	12 mmHg	1809.1	1303.2	474.6	437.2				
	7 mmHg	1950.0	2203.6	474.6	437.2	145.5	-616.3	907.3	0.71
Clusterin (pg/ml)	12 mmHg	218158.5	228839.5	28055.1	60547.5				
	7 mmHg	224658.7	389323.9	28055.1	60547.5	6710.4	-128957.0	142377.8	0.92
Calbindin (pg/ml)	12 mmHg	32585.9	32088.9	14389.3	26922.6				
	7 mmHg	26270.9	35330.9	14389.3	26922.6	-4654.0	-18497.1	9189.2	0.51

Table 2 Urinary Biomarkers in robot-assisted radical prostatectomy (RARP) Patients: comparing low= 7 mmHg vs standard= 12 mmHg Pneumoperitoneum (Pnp)

This table presents the mean and standard deviation (SD) of various urinary biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), vascular endothelial growth factor (VEGF), osteoactivin, kidney injury molecule-1 (KIM-1), clusterin, and calbindin, measured before and after RARP in patients who underwent surgery with either 7 mmHg or 12 mmHg pneumoperitoneum. The table also provides the mean difference between the two groups, along with their 95% confidence intervals (CI), and p-values to determine the statistical significance of the differences.

	Low Pnp(95%CI)	**Standard Pnp(95%CI)**	**Difference from standard Pnp (95% CI)**	***p***
U. Cloride	36.3 (31.1-41.4)	42.8 (34.7-50.8)	-6.5 (-15.9-2.9)	0.17
U. K	38.8 (31-46.6)	43.6 (36.2-51)	-4.8 (-15 -5.5)	0.35
U. Na	32.5 (27.7-37.4)	39 (31.7-46.3)	-6.4 (-15-2.1)	0.13
ACR	1.9 (1.3-2.5)	2 (1.3-2.6)	-0.03(-0.9-0.8)	0.93

Table 3 Urinary Electrolyte Analysis in robot-assisted Radical Prostatectomy (RARP) Patients: Comparing Low=7 mmHg vs. Standard=12 mmHg Pneumoperitoneum

This table presents the mean and 95% confidence interval (CI) of various urinary electrolyte parameters, including urinary chloride (U. Chloride, mmol/L), urinary potassium (U. K, mmol/L), and urinary sodium (U. Na, mmol/L), as well as the albumin-to-creatinine ratio (ACR, mg/mmol) for patients undergoing robot-assisted radical prostatectomy (RARP)with either low or standard Pnp. The differences between the two groups, along with their 95% CI, and p-values, are provided to determine the statistical significance of the differences.

	Standard Pnp	Low Pnp	p
Intra-op Urine Prod.	100 (50-200)	200 (100-325)	0.01
I.V. fluid infusion	1418 (341)	1474 (412)	0.46
2-hr Urine Prod.Post-surgery	200(100-300)	300 (200-500)	0.0008
Total Urine Prod. (1POD)	1000(850-1287)	1325(1025-1800)	0.001
S.creatinine (1POD)	98.9 (25.2)	93.6 (25)	0.29
eGFR (1POD)	70.7(16.5)	74.8 (15.5)	0.20
S.creatinine (10POD)	88 (18.6)	82 (15.7)	0.08
eGFR (10POD)	76.4 (13.6)	80 (10.7)	0.14

Table 4 Renal Function Parameters in robot-assisted radical Prostatectomy (RARP) Patients: Comparing Low=7 mmHg vs. Standard=12 mmHg Pneumoperitoneum

This table presents the median and interquartile range (IQR) or mean and standard deviation (SD) of various intra-operative and post-operative parameters related to urine production, fluid infusion, and renal function in patients undergoing robot-assisted radical prostatectomy (RARP) with either standard or low Pnp. P-values are calculated to determine the statistical significance of the differences between the two groups. I.V.=Intra venous, POD=post-operative day, eGFR= estimated Glomerular Filtration Rate.

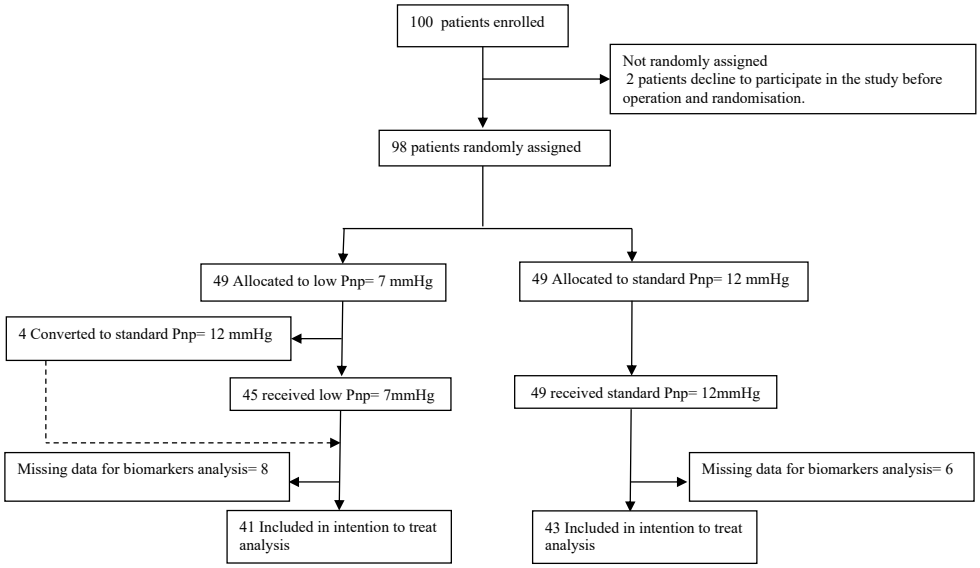

Fig1 Trial profile

Appendix D. Questionnaire in English

PART A

How have you been feeling in the last 24 hours?

(0 to 10, where: 0 = none of the time [poor] and 10 = all of the time [excellent])

1.	Able to breathe easily	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
2.	Been able to enjoy food	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
3.	Feeling rested	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
4.	Have had a good sleep	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
5.	Able to look after personal toilet and hygiene unaided	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
6.	Able to communicate with family or friends	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
7.	Getting support from hospital doctors and nurses	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
8.	Able to return to work or usual home activities	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
9.	Feeling comfortable and in control	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time
10.	Having a feeling of general well-being	None of the time 0 1 2 3 4 5 6 7 8 9 10 All of the time

PART B

Have you had any of the following in the last 24 hours?

(10 to 0, where: 10 = none of the time [excellent] and 0 = all of the time [poor])

11.	Moderate pain	None of the time 10 9 8 7 6 5 4 3 2 1 0 All of the time
12.	Severe pain	None of the time 10 9 8 7 6 5 4 3 2 1 0 All of the time
13.	Nausea or vomiting	None of the time 10 9 8 7 6 5 4 3 2 1 0 All of the time
14.	Feeling worried or anxious	None of the time 10 9 8 7 6 5 4 3 2 1 0 All of the time
15.	Feeling sad or depressed	None of the time 10 9 8 7 6 5 4 3 2 1 0 All of the time

Appendix E. Questionnaire in Danish

Du bedes sætte én cirkel rundt om det tal der passer bedst til udsagnet.

DEL A

Hvordan har du haft det de sidste 24 timer?

0 til 10, hvor 0 = på intet tidspunkt [dårligt] og 10 = hele tiden [fremragende]

1.	I stand til at trække vejret ubesværet	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
2.	Været i stand til at nyde mad	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
3.	Følt mig udhvilet	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
4.	Har sovet godt	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
5.	I stand til selv at klare personlig pleje og hygiejne	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
6.	I stand til at kommunikere med venner eller familie	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
7.	Fået den nødvendige støtte fra læger og sygeplejersker	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
8.	I stand til at genoptage arbejde eller normale hjemlige aktiviteter	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
9.	Følt mig veltilpas og i kontrol	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden
10.	Haft en følelse af generel velvære	På intet tidspunkt	0	1	2	3	4	5	6	7	8	9	10	Hele tiden

DEL B

Har du oplevet følgende indenfor de sidste 24 timer?

10 til 0, hvor 10 = på intet tidspunkt [fremragende] og 0 = hele tiden [dårligt]

11.	Moderate smerter	På intet tidspunkt	10	9	8	7	6	5	4	3	2	1	0	Hele tiden
12.	Svære smerter	På intet tidspunkt	10	9	8	7	6	5	4	3	2	1	0	Hele tiden
13.	Kvalme eller opkastninger	På intet tidspunkt	10	9	8	7	6	5	4	3	2	1	0	Hele tiden
14.	Følt mig bekymret eller ængstelig	På intet tidspunkt	10	9	8	7	6	5	4	3	2	1	0	Hele tiden
15.	Følt mig trist eller deprimeret	På intet tidspunkt	10	9	8	7	6	5	4	3	2	1	0	Hele tiden

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