

# MJA

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## I.V. Paracetamol

### БЕЗБЕДНА АНАЛГЕЗИЈА

менаџирање на болка кога сте загрижени за безбедноста



I.V. paracetamol за прв пат во Европа е применет во 2001 година, а денес поради неговата докажана безбедност и ефикасност е прв од избор **аналгетик и антипиретик**.

#### Предоперативна и Интраоперативна Аналгезија:

Предоперативна аналгезија е дефинирана како третман кој што започнува пред оперативниот зафат се со цел да се превенира воспоставувањето на централна сензибилизација на болка.

i.v. paracetamol е безбеден, добро толериран лек со докажана ефикасност како **предоперативна и интраоперативна аналгезија** за умерена до средна болка при оперативни зафати.

**Голем број на клинички студии** ја докажуваат ефикасноста на i.v. paracetamol како **предоперативна и интраоперативна аналгезија**.

#### КЛИНИЧКА СТУДИЈА:

Ефект од **предоперативен i.v. paracetamol** за постоперативни аналгетски потреби кај пациенти кои се подложни на оперативни зафати. A Sreenivasulu, R Prabhavathi, 2015

**Цел:** Да се утврди ефикасноста на **предоперативната употреба на 1000mg i.v. paracetamol** кај постоперативните болки и аналгетски потреби кај пациенти подложни на хируршки зафати.

**Метод:** 60 пациенти беа поделени во две рандомизирани групи од по 30 пациенти.

**На I. Група** им беше администрирано **ампула од 1000mg i.v. paracetamol разредена 0,9%NaCl** p-ор 30 минути пред индукција (**ГРУПА П**),

**На II. Група** им беше администрирано **i.v. 0,9% NaCl** p-ор **100мл** 30 минути пред индукција (**ГРУПА НС**)

Сите пациенти беа индуцирани со i.v. thiopentone 5mg/kg, i.v. fentanyl 2µg/kg, i.v. vecuronium 0.1mg/kg

Постоперативниот резултат на болка беше мерен со **Визуелна Аналогна Скала (ВАС) од "0-10"**. Исто така беше забележувана и **постоперативната употреба на tramadol** како спасувачки аналгетик. Инциденцата на **постоперативно гадење и повраќање (ПОПП)** и други компликации исто така беа забележувани во пост оперативниот период.

**Резултатот** на постоперативната болка беше забележуван во интервали 15 мин, 30 мин, 1 час, 2 часа, и 6 часа.

**Заклучок:** Предоперативна администрација на **1000mg i.v. paracetamol** кај пациенти подложни на оперативен зафат обезбедува **статистички задоволителна аналгезија**, и ја **намалува постоперативната употреба на tramadol**. Оттука **1000mg i.v. paracetamol** може безбедно да се администрира како превенција при оперативни зафати.

#### Резултат:

**Табела 1:** Споредба на средниот резултат на болка (ВАС) помеѓу двете групи

Интервали	I Група П	II Група НС	P вредност
15 мин	2.06 ± 0.63	2.61 ± 0.56	0.0006
30 мин	2.35 ± 1.17	3.84 ± 1.55	0.0001
1 час	2.42 ± 1.12	2.87 ± 0.99	0.0989
2 часа	2.13 ± 1.06	2.52 ± 0.89	0.1219
6 часа	2 ± 0.52	2.52 ± 0.89	0.0549

**Табела 2:** Споредба за потребите од tramadol помеѓу двете групи

Интервали	I Група П	II Група НС	P вредност
До 1 час	4 (12.90%)	15 (50%)	0.0002
1-2 часа	3 (9.68%)	2 (6.45%)	0.64
2-6 часа	1 (3.23%)	3 (9.68%)	0.301
<b>Вкупно</b>	<b>8 (25.81%)</b>	<b>20 (64.52%)</b>	<b>0.002</b>

**Табела 3:** Споредба на ПОПП помеѓу двете групи

ПОПП	
I Група П	II Група НС
0	4

i.v. Paracetamol + јак опоид	<b>МНОГУ ЈАКА БОЛКА</b>
i.v. Paracetamol + слаб опоид	<b>ЈАКА БОЛКА</b>
i.v. Paracetamol + NSAID i.v. Paracetamol + rescue medicine	<b>УМЕРЕНА БОЛКА</b>
i.v. Paracetamol + rescue medicine	<b>СЛАБА БОЛКА</b>

**Мултимодално менаџирање на постоперативна болка**  
**I.V. Paracetamol** е атрактивна компонента за мултимодално менаџирање на болка.

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- Намалување на несаканите ефекти поврзани со монотерапија на NSAID и опоидни лекови
- Ублажување на акутна и хронична болка

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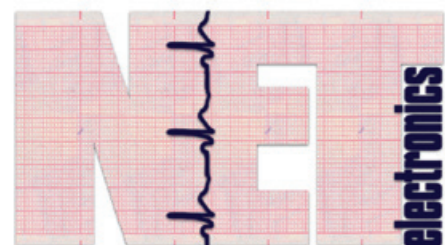
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## MYOCARDIAL INJURY AFTER NON-CARDIAC SURGERY: IS THERE A REASON FOR CONCERN?

*Vavlukis Marija, MD, PhD, FESC*

*University Clinic of Cardiology, Faculty of Medicine, University Ss Cyril and Methodius, Skopje, Macedonia*

Perioperative myocardial injury truly represents an “eclipsed epidemic”, especially because it is loudly “silent”, characterized by absence of the classical clinical symptom of chest pain due to anesthesia, sedation, or pain-relieving medications (1). Myocardial injury after non-cardiac surgery (MINS) is defined as a postoperative troponin elevation without a clear non-cardiac cause. The incidence ranges from 5 to 25% of the patients undergoing non-cardiac surgery, with about 90% of them being asymptomatic (2, 3). However, this condition is associated with increased post-operative mortality. The discovery of MINS is a new challenge for anesthesiologists, as well as for cardiologists, as a new opportunity to improve the outcome in surgical patients (4). Major non-cardiac surgeries, as defined by the Canadian Cardiovascular Society (surgeries requiring overnight hospital admission), are estimated to be >200.000.000/yearly/ worldwide and >10.000.000 of them are accompanied by some major cardiovascular (CV) complication: cardiovascular death, cardiac arrest, myocardial injury/infarction. Among all CV complications associated with non-cardiac surgery, perioperative myocardial infarction (PMI), and/or myocardial injury during non-cardiac surgery (MINS), have a leading role (5, 6).

### What is the difference between PMI and MINS?

According to the fourth MI universal definition, PMI is defined as post-operative cardiac troponin (cTn) elevation, within a period of 30 days after non-cardiac surgery, with a typical rising and/or falling cTn pattern, with an underlying ischemic origin (absence of non-ischemic etiology such as rapid atrial fibrillation, pulmonary embolism, sepsis, etc.), accompanied by an ischemic ECG pattern, with or without symptoms (7). PMI represents a smaller proportion of ischemia/injury events that can develop as type 1 or type 2 MI. Type 1 PMI scenario describes a sudden rupture of a vulnerable coronary plaque (in 50 – 60% of patients), platelet aggregation or severe coronary vasospasm, causing either occlusive (ST-segment elevation, STEMI) or non-occlusive (non-ST-segment elevation, NSTEMI) thrombus, while type 2 PMI describes a scenario of supply-demand mismatch (2, 7). MINS is a myocardial injury based on ischemia, irrespective of developing necrosis, accompanied by an increased cTn level, but it does not fulfill the universal PMI definition (regarding cTn level/dynamic, and absence of typical ECG patterns and symptoms). The hs-cTn threshold for MINS diagnosis is either at least 5ng/L increase, when basal value ranges from 20 to 65ng/L, or hs-cTn level  $\geq 65$ ng/L. A common criterion for both conditions is absence of non-ischemic etiology troponin elevation (pulmonary embolism, sepsis, renal failure,

cardioversion etc.) (1, 7, 8). The clinical significance is the combined effect of frequency and increased incidence of 30-days and one-year mortality (1, 7, 8). MINS and PMIs are among the most frequent cardiovascular peri-and post-operative complications (6).

The underlying pathophysiological mechanisms that increase the propensity for MINS are a conglomeration of various factors such as: pre-existing medical condition, high-risk surgical interventions, intraoperative hemodynamic instability and postoperative care (1, 8). Proposed disease – and operation-activated mechanisms are: a myocardial demand-supply mismatch (result of hemodynamic instability, hypotension, rapid fluid shifts, acute blood loss), mainly occurring during emergency surgeries; increased cardiac metabolic demand that may lead to MI in patients with otherwise stable CAD; destabilization of a preexisting atherosclerotic plaque in the perioperative period due to fissuring or rupture, resulting with distal thrombus embolization, or small coronary artery thrombosis as a result of a hypercoagulable state (activated thrombogenic factor), activated inflammatory milieu, etc. (1, 2, 3, 4, 8, 9). Type of anesthesia was also considered a contributive factor, however, the study of Kwon demonstrated that the type of anesthesia has no significant role in the development of MINS (10).

It is considered that every fourth patient who undergoes non-cardiac surgery will develop myocardial injury/infarction, with a reported MINS incidence of approximately 18-25%. Within MINS, the incidence of PMI ranges from 0.3 to 16%, or when an hs-cTn assay is employed, about 20-30% of MINS are patients with PMI (7). PMI carries a similar 30-days mortality risk for symptomatic and asymptomatic patients (aOR 4.00; 95% CI, 2.65-6.06 and aOR 4.76; 95% CI, 2.68-8.43 respectively) (6). Magoon et al. reported a high in-hospital mortality (12-40%) of the patients who developed PMI during non-cardiac surgery (1). MINS was associated with an insignificantly lower aOR of 3.30 (95% CI, 2.26-4.81), or as reported by Sharma et al., up to 10% of patients will develop MINS, with an exponential incidence rise as a function of the peak postoperative hs-cTn concentration (2). In the post-operative period, the possibility of missing the diagnosis of MINS is due to the lack of symptoms and typical ECG changes. The majority of PMIs occur within the first 48 hours, while the patient is still on analgesic medications, which is one of the reasons why 65% of patients are without ischemic symptoms (6). Having this said, one can appreciate the role of serial cardiac troponin measurement, and a joint guidance for the best treatment decision-making for this patient cohort (2, 6). Pre-operative cardiac risk assessment aims towards estimation of the surgery risks/benefits, guiding management decisions (ex. endovascular vs. open surgery), and modulation of the need for pre-, peri-and post-surgery monitoring. Four key points of the evaluation are: pre-operative cardiac risk assessment, peri-operative cardiac risk modification, and monitoring and management of the peri-operative cardiac complications (6, 11, 12).

### Diagnosis of MINS

Cardiac troponin (cTn), especially high sensitivity assays (hs-cTn), enables identification of high-risk patients undergoing non-cardiac surgery. Baseline values knowledge identifies patients

with chronic elevation, who are at increased peri-and post-operative risk. Approximately 35% of post-operative patients will have levels of hs-cTn above the 99th percentile URL, and 17% an elevation and a rising pattern indicative of evolving PMI. Patients with a rising pattern are at particular risk; the greater the rise, the greater the risk (7). According to the latest (CCS) guidelines for CV evaluation before non-cardiac surgery, individuals >44 years, or 18-44 years with known significant CV disease, who undergo major non-cardiac surgery, have an indication for clinical risk estimation, followed by cardiac biomarkers, as needed (6). Opposite to the generally accepted approach in our surgical-anesthesiologic milieu, where resting echocardiography is the first reached tool after clinical risk assessment, pre-operative measurement of natriuretic peptides (NT-proBNP or BNP) is the second step recommended for patients >65 years, or 45-64 years with known significant CV disease, or with a Revised Cardiac Risk Index (RCRI)  $\geq 1$  (5, 6, 13). Post-operative cTn surveillance is recommended for high-risk individuals. In order to properly interpret the etiology of elevated post-operative values, a baseline pre-operative value is necessary to determine whether the increase is acute or chronic. However, a MI diagnosis still requires serial cTn measurement in the first 2-3 post-operative days, as PMIs usually develop during this period, in conjunction with ECG monitoring (7). Data from the VISION and CHASE trials strongly supports the recommendation of obtaining daily troponin measurements for 48-72 hours after non-cardiac surgery. The serial measurement is recommended for patients with an increased baseline risk (patients with elevated NTproBNP/BNP levels before surgery/or in those who have an RCRI score  $\geq 1$ /or aged 45-64 years with significant cardiovascular disease/ or aged  $\geq 65$  years) (6). The presence of cTn elevation should guide risk optimization and peri-operative monitoring of non-cardiac surgery patients, as cardiac and non-cardiac causes of cTn elevation are associated with increased mortality. Thus, cTn may be used as a prognostic tool for patients who are critically ill, with the understanding that troponin elevation is a prognostic indicator of severity of illness and does not directly correlate to ischemic heart disease (4).

### Proof of the Concept

The association between small cTn increase and peri-/post-operative outcome was described by Landesberg in 2003. MINS was increasingly popularized by the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) group of investigators. VISION investigators defined MINS in the presence of peak hs-cTn T >30ng/L due to myocardial ischemia. It was observed in 8% of patients, 84% of whom were asymptomatic, and was associated with an increased 30-days mortality (9.8% vs. 1.1%). This “high risk” group of patients was detected through routine serial measurement of post-operative cTn. Pick hs-cTn T levels within 20-65ng/L with an absolute change >5ng/L, without ischemic features, were a strong independent predictor of 30-days all-cause mortality (HR: 3.20; 95% CI: 2.37-4.32). The risk for all-cause mortality continued over the first post-operative year (OR: 6.7; 95% CI: 4.1-10.9). Elevated hs-cTn was identified as a strong independent predictor of 30-days mortality. (1, 4, 6, 8, 13) The ENIGMA II trial

investigators supported the VISION study results. MINS patients experienced higher one-year mortality rate in comparison to those without MINS (10.6% vs. 4.6%,  $p < 0.001$ ). However, one has to be aware that patients in the ENIGMA II Trial underwent two different types of anesthesia (data should be considered with precaution) (8). The significant difference between the VISION and CHASE (Cardiac Health After Surgery) trials is the fact that in the CHASE trial hs-cTn I was measured, which is less influenced by renal function, and alignment was made not only for age and sex, but for pre-operative renal function as well. The only two independent variables associated with 30-days mortality were emergency of the operation and troponin levels. Higher values were associated with higher hazard ratios in three hs-cTn I range groups ( $\leq 60\text{ng/L}$ ; 70-590ng/L, and  $\geq 600\text{ng/L}$ ) with respective HRs (HR 2.36; 95% CI 1.31-4.22 and 4.19; 95% CI 2.06-8.55) for the second and third as compared to the first group. (9, 14) Ekeloef and coworkers reported a significant risk of MINS after major emergency abdominal surgery. Nearly one quarter (24.4%) of patients demonstrated myocardial injury within the third post-operative day. Advanced age was identified as a significant independent risk factor (adjusted OR: 2.2; 95% CI 1.7-2.9;  $p < 0.0001$ ), besides cTn level (15). Lee et al. reported an 8-13% MINS incidence, depending on the risk of non-cardiac surgery. That means that even high-risk patients for MINS (patients with obstructive sleep apnea), undergoing low risk non-cardiac surgery (elective knee arthroplasty) will have a low MINS incidence (16). As commented by Rich in his review of the VISION and CHASE studies, even “small troponin leaks” in older adults undergoing non-cardiac surgery are independently associated with increased 30-days postoperative mortality. The interrelation between non-cardiac surgery (specifically if urgent), older age ( $>65$  years) and small troponin increase is a “deathly trio” that should be taken into consideration when treating such patients (9).

### Prevention and Management of MINS

At the present moment there is no clear recommendation for the therapeutic treatment of MINS. In the Guidelines of the Canadian Cardiovascular Society, the use of aspirin and statin is recommended (Class I recommendation, Level B evidence), for their pleiotropic effects (6, 4). However, the aspirin treatment should be put in context with frequent use of NSAID and LMWH, and increased risk of bleeding in this fragile patient population (9). The role of beta blockers and RAAS system blockers is questionable at this point. Beta blockers may improve the supply/demand mismatch; however, the benefits must be weighed against the risk of hypotension, which may accentuate the myocardial injury (4). The MANAGE trial reported potential beneficial effects of dabigatran, requesting further investigation (4, 17).

Prevention strategies should be based on the proposed pathophysiological mechanisms of MINS: a balance between adequate antithrombotic treatment, without increasing the risk of bleeding, and minimization of the adverse effects of increased sympathetic drive while avoiding hypotension (beta-blockers, RAAS blockers) (4). Again, the cornerstone prevention seems to be aspirin and statins, supporting the data from the studies of George et al. and Berwanger et

al., with the recommendation that they should be initiated at least two weeks prior to surgery to benefit from their plaque stabilizing and anti-inflammatory effects (4). All three major guidelines recommend continuing statin therapy in the peri-operative period (Class I recommendation, Level C evidence) (1, 4, 6, 11, 12, 18). Due to discouraging results from the POISE and DECREASE trials with beta-blockers, initiation of antihypertensive agents in the immediate pre-operative period is discouraged. Chronic antihypertensive medications should be optimized (4). Future treatments are switching from traditional cardiomyocentric treatments in peri-operative cardio-protection, to non-myocyte cell cardio-protection. Nowadays, epi-genetic regulation of cardiac response to stressors seems one of the most promising approaches of acute peri-operative cardio-protection (18).

In conclusion, MINS is a frequent and clinically significant adverse effect of non-cardiac surgery, associated with increased risk of early post-operative mortality. The diagnostic/therapeutic approach to MINS is a challenge for anesthesiologists, bearing in mind the lack of widespread knowledge of the condition, and having no evidence-based therapeutic treatment options. This makes it a challenge for anesthesiologists and cardiologists for further joint research studies.

**Conflicts of interest:** None

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## RIGHT VENTRICULAR E/E' RATIO INDEX FOR INTRAOPERATIVE ASSESSMENT OF RIGHT VENTRICULAR FILLING PRESSURE IN MITRAL VALVE SURGERIES WITH PULMONARY HYPERTENSION

*Abdlaziz I, Ashmawi H, Idris D, Hafez H*

*Department of Anaesthesia, Cairo University Hospitals, Faculty of Medicine, Cairo University*

### ABSTRACT

**Introduction:** Diastolic dysfunction is an underestimated pathology with a high risk of acute decompensation during the perioperative period. There is sufficient evidence to support the significant prevalence of perioperative diastolic dysfunction and its incidence following the cardiac surgery.

**Material and Methods:** Measuring of the hemodynamic and echocardiographic parameters of Right ventricular diastolic function: E, e', RV E/e', Tricuspid annular plane systolic excursion (TAPSE) and Systolic pulmonary artery pressure (SPAP) in 40 adult patients with pulmonary hypertension more than 50mmHg undergoing mitral valve surgery in four intraoperative occasions: after sternotomy, immediately after weaning from cardiopulmonary bypass (CPB), 10 minutes after CPB and after chest closure.

**Results:** There was a positive correlation between Right Ventricular E/e' ratio and systolic pulmonary artery pressure (SPAP) (r=0.72, p=0.000), a positive correlation between Right Ventricular E/e' ratio and right atrial pressure (RAP) (r=0.47, p=0.0043) and a negative correlation between Right Ventricular E/e' ratio and Tricuspid annular plane systolic excursion (TAPSE) (r=-0.53, p=0.001).

**Conclusion:** RV E/e' positively correlates with right atrial pressure, Systolic pulmonary artery pressure and negatively correlates with Tricuspid annular plane systolic excursion (TAPSE) which makes it a potentially useful index for assessing Right Ventricular systolic function in the operative setting.

**Key Words:** *Central venous pressure (CVP), Diastolic Dysfunction, Right Ventricular E/e', Systolic pulmonary artery pressure (SPAP), Tricuspid Annulus Plane Systolic Excursion (TAPSE).*

## Introduction

Patients with long standing mitral valve disease are at risk of developing pulmonary hypertension, which may present a great challenge to the cardiac anaesthetist during cardiac surgery (1). Pulmonary hypertension is an important risk factor for the development of acute right-sided heart failure (2). The right ventricle (RV) dilates in response to chronic volume and/or pressure overload, and RV end-diastolic diameter has been identified as a predictor of survival in patients with chronic pulmonary disease (3).

Strategies to reduce pulmonary vascular tone aims to enrich vascular smooth muscle with cyclic Adenosine Monophosphate (cAMP) through beta agonists (e.g. Isoprotrenol) or with phosphodiesterase type III inhibitors (e.g. milrinone). Alternatively, by increasing cyclic Guanine Monophosphate (cGMP) with nitroso vasodilators (sodium nitroprusside, nitroglycerine, inhaled Nitric Oxide), also reduces pulmonary vascular tone (4,5).

The ratio between the early diastolic pulsed Doppler velocities of the mitral inflow (E) and the basal left ventricular (LV) tissue (e) is a suggested new tool in the identification of an elevated left ventricular filling pressure (LVFP) (6).

Among non-invasive filling variables, the E/e' index >15 was shown by Ommen et al. to be the single best predictor of an elevated LVFP, to have a high specificity and also to point to an adverse outcome (7).

When LVFP is elevated, the pressure difference, physiologically required for blood flow, is maintained by increased pressure generated from the right ventricle (3). However, the use of Right ventricular RV E/e' ratio for assessing right ventricular filling pressure and diastolic function has yet to be investigated.

## Material and Methods

Following the approval by departmental ethics and research committee of Faculty of Medicine Cairo University, and obtaining informed consent, the study was conducted on 40 patients who scheduled for mitral valve surgery in Kasr Alaini teaching hospital in adult cardiac surgery department.

Inclusion criteria:

1. Adult patients, aged 16 – 60 years old, scheduled for mitral valve surgeries (replacement or repair).
2. Males and females.
3. Presence of pulmonary hypertension (above 50mmHg) on the preoperative transthoracic echocardiogram (TTE), as a predisposing factor for right ventricular diastolic dysfunction.

Exclusion Criteria:

1. Patients younger than 16, or older than 60 years old.
2. Patients with ischemic mitral valve disease.
3. Left ventricular ejection fraction below 45%.

4. Associated significant aortic or tricuspid valve disease.
5. Patients with clinically significant chest infection or chronic obstructive pulmonary disease (COPD).

## Technique of anaesthesia

Induction of anaesthesia was achieved by propofol 1-2mg/kg, Fentanyl 1-2µg/kg, and pancuronium 0.1mg/kg, to facilitate endotracheal intubation and provide muscle relaxation. Maintenance was achieved by supplemental doses of fentanyl to be given in anticipation of painful stimuli (e.g. skin incision, sternotomy, sternal retraction, and pericardiotomy) with a total dose of 10 - 15µg/kg). Isoflurane 0.5 – 1.5 MAC was administered to provide hypnosis and facilitate hemodynamic control. Additional doses of pancuronium was administered according to clinical needs. All patients were intubated and mechanically ventilated using volume-controlled ventilation with a tidal volume of 6mL/kg, and a respiratory rate 16 breath/min, using FiO<sub>2</sub> of 0.6 in air. Re-adjustment of respiratory rate and FiO<sub>2</sub> was done after blood-gas analysis to maintain PaCO<sub>2</sub> between 30 – 35mmHg, and PaO<sub>2</sub> between 200 – 300 mmHg.

Intraoperative monitoring included 5-lead ECG, end-tidal capnography, pulse oximetry, invasive blood pressure, and central venous pressure. Intraoperative transesophageal echocardiography (TEE) was performed. Before the initiation of cardiopulmonary bypass, anticoagulation was achieved by the administration of heparin at a dose of 4mg/kg and was targeted to obtain activated coagulation time (ACT) >450 seconds to be checked after 3 minutes from giving heparin.

At the start of the CPB, milrinone was started at a loading dose of 50µg/kg by IV push over 10 minutes, then continuous infusion (0.375-0.75µg/kg/min) and was continued in the post-bypass period and into the ICU. Noradrenaline (0.02-0.2µg/kg/min) was added in cases that had mean blood pressure less than 60mmHg.

After completion of the surgical procedure, return to normothermia, and adequate debubbling of the heart, mechanical ventilation was reinstated and weaning from CPB was attempted. At the end of surgery, and after wound closure, patients were transferred to the ICU to be weaned from drug infusions and mechanical ventilation according to our standard ICU protocol.

Data Collection:

- Transesophageal echocardiography and hemodynamic data were collected at 4 intervals during surgery: After sternotomy (T0), immediately after weaning from CPB (T1), 10 minutes Post-CPB (T2) and after chest closure (T3).
- Hemodynamic data: Heart rate (beat/min), Systolic, diastolic and mean blood pressure (mmHg) and Central venous pressure (mmHg)
- Transesophageal echocardiographic examination:

All TEE images and clips were recorded for offline analysis. Intraoperative transesophageal echocardiography was performed with the aid of a multiplane esophageal transducer (GE medical



system, Milwaukee, Wisconsin 53201 USA). Analysis was done using the software included in the system. In each patient, the examination proceeded as follows:

1. Tricuspid inflow early (E-wave) velocity was obtained in the midesophageal 4-chamber view and the transgastric RV inflow view, with the sample volume located at the tips of the tricuspid leaflets. The higher reading was recorded and considered the more accurate.
2. Tissue Doppler analysis of the tricuspid annulus was obtained in the midesophageal 4-chamber view. Using pulsed-wave Doppler by utilizing the built-in TDI option of the machine, the sample volume was placed onto the lateral myocardial wall of the tricuspid annulus. Early diastolic wave (e'-wave) velocity was measured.
3. E/e' ratio for the right ventricle was calculated.
4. Tricuspid annular plane systolic excursion (TAPSE): TAPSE measures the longitudinal systolic motion of the free edge of the tricuspid valve annulus. It was measured using M-mode imaging in the four-chamber view, typically on the lateral annulus.
5. Pulmonary artery systolic pressure (mmHg), SPAP was calculated by the aid of transeophageal echo Doppler as follows:  $SPAP = \text{Right ventricular systolic pressure (RVSP)} + \text{right atrial pressure (CVP)}$ . For quantitative assessment of RVSP, the peak tricuspid regurgitant (TR) jet velocity, obtained on continuous wave Doppler, was used to calculate peak pressure gradient between RV and RA during systole using the modified Bernoulli's equation,  $\Delta p = 4 \times V^2$  where  $\Delta p$  is the pressure gradient and V is the maximal velocity of the tricuspid regurgitant jet.

## Results

The study was conducted on 40 adult patients (16-60 years old) who underwent elective mitral valve surgery with CPB in Kasr Alaini teaching hospital in adult cardiac surgery department. All patients had pulmonary hypertension (above 50mmHg) measured by the preoperative transthoracic echocardiogram (TTE), as a predisposing factor for right ventricular diastolic dysfunction. Demographic and preoperative data are presented in table 1.

**Table 1:** Demographic and preoperative data

Age (years)	31.09 + 7.25
Sex (M/F)	26/14
Weight (Kg)	80.55 + 12.15
Height (cm)	165.73 + 9.25
BSA	1.95 + 0.23
EF (%)	55.18 + 5.56
FS (%)	28.91 + 4.08
SPAP (mmHg)	75.45 + 10.83
Predominant Lesion (MS/MR)	29/11

(Data are presented as  $M \pm SD$  or ratio. BSA: Body surface area, EF: Ejection fraction, FS: fractional shortening, SPAP: Systolic pulmonary artery pressure, MS: Mitral stenosis, MR: Mitral regurgitation)

**Table 2:** Hemodynamic parameters

	T0	T1	T2	T3
RV E	74.71 + 9.51	75.03 + 9.71	67.74 + 9.34*	62.76 + 9.50*
RV e'	8.31 + 1.83	8.68 + 1.36*	9.48 + 1.78*	9.411 + 1.61*
E/e'	9.40 + 2.24	8.76 + 1.17*	7.34 + 1.46*	7.09 + 1.62*
TAPSE (cm)	1.17 + 0.20	1.29 + 0.18*	1.44 + 0.12*	1.41 + 0.09*
SPAP (mmHg)	78.86 + 15.05	64.09 + 11.47*	55.20 + 6.35*	49.20 + 4.95*

(Data are presented as  $M \pm SD$ . \*:  $p < 0.05$  compared to baseline. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial blood pressure, HR: Heart rate, CVP: Central venous pressure)

Intraoperative transoesophageal echocardiography (TEE) data were taken in four occasions (see before). Adjustment of the alignment of the Doppler beam for obtaining the most accurate results were failed in 5 cases. Therefore, they were excluded from the study and results were obtained from the remaining 35 cases. TEE parameters are listed in table 3.

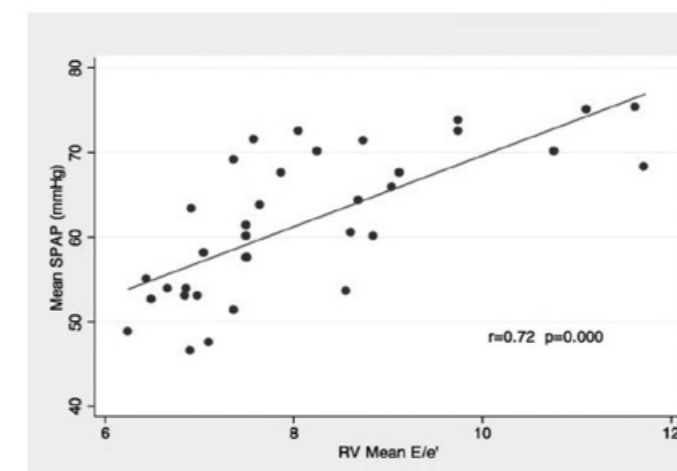
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	T0	T1	T2	T3
RV E	74.71 + 9.51	75.03 + 9.71	67.74 + 9.34*	62.76 + 9.50*
RV e'	8.31 + 1.83	8.68 + 1.36*	9.48 + 1.78*	9.411 + 1.61*
E/e'	9.40 + 2.24	8.76 + 1.17*	7.34 + 1.46*	7.09 + 1.62*
TAPSE (cm)	1.17 + 0.20	1.29 + 0.18*	1.44 + 0.12*	1.41 + 0.09*
SPAP (mmHg)	78.86 + 15.05	64.09 + 11.47*	55.20 + 6.35*	49.20 + 4.95*

(Data are presented as  $M \pm SD$ . \*:  $p < 0.05$  compared to baseline. RV E: Right Ventricular E wave, RV e': Right ventricular e' wave, RV E/e': Right Ventricular E/e' ratio, TAPSE: Tricuspid Annular Plane Systolic Excursion, SPAP: Systolic Pulmonary Artery Pressure)

Correlation between Right Ventricular Mean E/e' ratio (RV E/e') and Mean Systolic Pulmonary Artery Pressure (SPAP): There was a positive correlation between RV mean E/e' ratio and mean SPAP. ( $r=0.72$ ,  $p=0.000$ ), Figure 1.

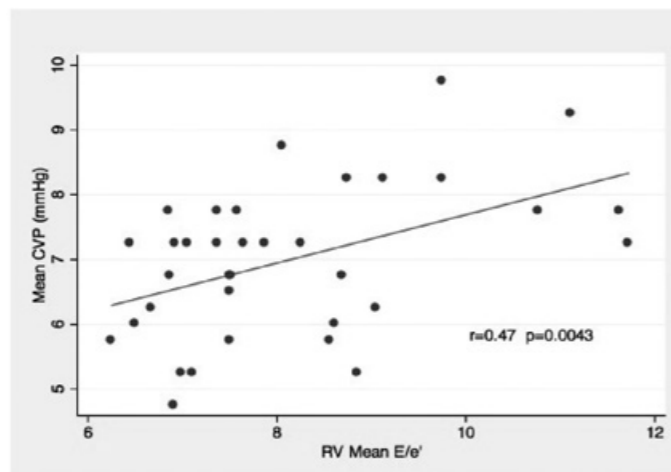
**Figure 1:** Scatter Plot graph of RV mean E/e' and mean SPAP



(RV mean E/e': Right ventricular mean E/e' ratio, Mean SPAP: Mean Systolic pulmonary artery pressure)

Correlation between Right Ventricular Mean E/e' ratio (RV E/e') and Mean Central Venous Pressure (CVP): There was a positive correlation between RV mean E/e' ratio and mean CVP ( $r=0.47$ ,  $p=0.0043$ ), Figure 2.

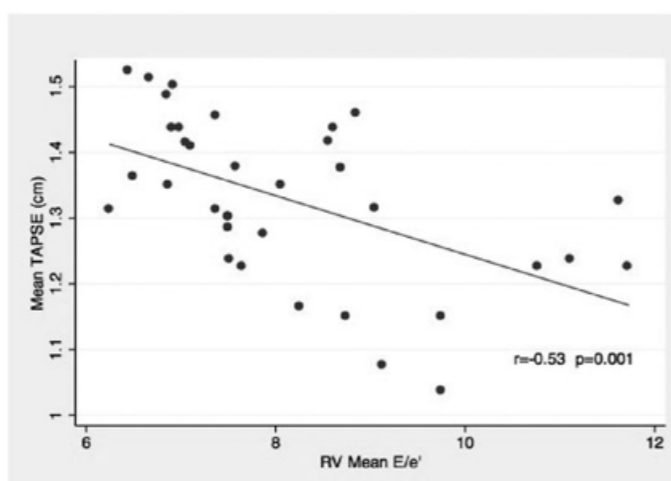
**Figure 2:** Scatter Plot graph of RV mean E/e' and mean CVP



(RV mean E/e': Right ventricular mean E/e' ratio, Mean CVP: Mean central venous pressure)

Correlation between Right Ventricular Mean E/e' ratio (RV E/e') and Mean Tricuspid Annular Plane Systolic Excursion (TAPSE): There was a negative correlation between RV E/e' ratio and TAPSE ( $r=-0.53$ ,  $p=0.001$ ), Figure 3.

**Figure 3:** Scatter plot graph of RV mean E/e' and TAPSE



(RV mean E/e': Right ventricular mean E/e' ratio, TAPSE: Tricuspid Annular Plane Systolic Excursion)

Regarding the clinical aspects and the inotropic use, all these results were collected from 40 adult patients who underwent mitral valve replacement surgeries. We routinely used milrinone 50µg/kg loading dose by IV push over 10 minutes, then continuous infusion (0.375-0.75µg/

kg/min) at the start of the CPB and was continued in the post-bypass period and into the ICU. Noradrenaline (0.02-0.2µg/kg/min) was added in cases that had mean blood pressure less than 60mmHg. Regarding Follow up of these patients in the ICU and thereafter, they showed no mortalities till their discharge from the hospital.

## Discussion

Diastolic dysfunction is an underestimated pathology with a high risk of acute decompensation during the perioperative period. There is sufficient evidence to support the significant prevalence of perioperative diastolic dysfunction and its incidence following cardiac surgery (8,9). In this study we measured the hemodynamic and echocardiographic parameters of right ventricular diastolic function in 40 adults with pulmonary hypertension undergoing mitral valve surgery.

The main findings in this study are that there was a positive correlation between RV E/e' and Right atrial pressure (RAP) (central venous pressure: CVP), a positive correlation between RV E/e' and Systolic pulmonary artery pressure (SPAP), and a negative correlation between RV E/e' and Tricuspid Annular Plane Systolic Excursion (TAPSE).

Takamura et al. (2010) studied the coupling between Left Ventricle (LV) contraction and relaxation in 40 patients. They used speckle tracking echocardiography. They concluded that global LV function revealed strong coupling of LV contraction to relaxation sequentially from normal to failing myocardium, regardless of their heterogeneous pathophysiology and that the extent of myocardial systolic shortening was the most powerful independent contributor of LV relaxation in both the longitudinal and circumferential directions. This study strongly showed that LV myocardial systolic contraction directly regulates its relaxation. In our study there was a significant linear negative correlation between RV E/e' and Tricuspid Annular Plane Systolic Excursion (TAPSE) which we assume to be due to the same mechanism (10).

Pirracchio et al. (2007) studied the diastolic function in anaesthesia and ICU and revealed that an increase in afterload induces a delay in the onset of relaxation and an increase in the time constant of isovolumetric relaxation ( $t$ , ms). The afterload-dependence of  $t$  has also been shown to be influenced by the inotropic state. Moreover, the concept of relative load was defined experimentally as the ratio of peak systolic LV pressure to peak isovolumetric pressure. The higher the relative load, the lower the contractile reserve. The contractile reserve quantifies the percentage force developed by the LV with respect to its maximum value. The consequences on relaxation of an elevation in LV afterload can range from a moderate acceleration to a marked deceleration, depending on the relative load. Up to a relative load of around 80%, the diastolic decline in LV pressure accelerates, but above this LV pressure decline decelerates. Acceleration of the LV pressure decrease in response to a load elevation is observed in the normal heart, whereas slowing of the LV pressure decline is associated with impaired cardiac function. This introduced the concept of afterload reserve which relates to the capacity of the normal LV to respond to elevation of afterload without changes in LV end-systolic volume and LV pressure

decline. Ventricles with altered contractile function consistently show a decreased “afterload reserve”. In such ventricles, even a small afterload elevation will cause a marked deterioration in LV relaxation and increase LV systolic and diastolic volumes (11). Our study showed a significant linear positive correlation between Right Ventricular E/e’ and systolic pulmonary artery pressure which we assume to be due to the same mechanism.

The development of right-heart failure in pulmonary hypertension is secondary to the pulmonary vasculopathy. Right-heart affection and failure is the immediate cause of death in the most of the patients with pulmonary hypertension (12).

A better understanding of the mechanisms underlying the transition from compensated right ventricular hypertrophy to maladaptive remodeling and dilatation could lead to the development of right ventricular-specific therapies, improving survival in pulmonary hypertension. Decreased cardiomyocyte contractility (related to re-expression of fetal-type contractile proteins and disturbances in Ca<sup>2+</sup> handling and energy generation) triggers autocrine, paracrine, and neuroendocrine signaling pathways that can either compensate the diminished force generation, or can lead to further deterioration. Unopposed Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) formation, inflammation, Right ventricular ischemia, and cardio-myocyte apoptosis contribute to the creation of a vicious circle that finally results in right-heart failure (12).

E/e’ has been investigated in several studies and has been shown to be a load-independent index. Giovanna Pela et al. (2004) assessed the influence of a progressive reduction of preload, obtained by Lower Body Negative Pressure (LBNP), on the diastolic and systolic myocardial waves compared to the inflow patterns estimated in the left and right ventricles in nine healthy subjects and revealed that myocardial E’, A’ and S’ velocities in both the left and right ventricle were significantly affected by preload in healthy patients and supported the usefulness of e’/a’ ratio as a relatively load-independent index of diastolic function (13).

Hemodynamic parameters have shown significant changes over the time during our study. This could be attributed to several factors including anesthesia, mechanical ventilation, surgery, and pharmacologic interventions. Because our patients were all suffering from severe pulmonary hypertension, active measures were taken to control pulmonary artery pressure according to our institutional protocol. We used milrinone with 50µg/kg loading dose by IV push over 10 minutes, then continuous infusion (0.3-0.7µg/kg/min). We added Noradrenaline infusion (0.02-0.2µg/kg/min) in cases with mean blood pressure less than 60mmHg. Among selective phosphodiesterase III inhibitors, milrinone is the most frequently used and has been shown to reduce pulmonary pressures and augment RV function in many studies in patients with pulmonary vascular dysfunction (14). In our study we used Noradrenaline infusion in 30 cases to overcome the effect of milrinone on systemic vascular resistance and to improve Mean arterial blood pressure (MAP).

Many studies focused in mitral E/e’ ratio and its validity and clinical significance. Hillis et al. (2004) studied 250 unselected patients 1.6 days after admission for myocardial infarction and found that non-invasive estimation of left ventricular filling pressure by mitral E/e’ ratio was a

powerful predictor of survival after acute myocardial infarction and that, in particular, an e/e’ ratio more than 15 would predict poorer survival after acute myocardial infarction (15).

Chikako Yoshida et al. (2009) assessed the comparative value of measurements of tissue Doppler early diastolic mitral annular velocity (E’), left atrial diameter (LAD), and left atrial volume (LAV) in 91 patients with all three of the followings: Heart failure (HF), LVEF of greater than 55%, and normal mitral E/A ratio between 0.8 and 1.5 and used twenty healthy subjects as controls, and found that LAV and LAD indexes are more useful in detecting with HF and normal Ejection Fraction (EF) patients than E’ related parameters (16).

In spite of the promising results for mitral E/e’, a controversy still exists regarding its value in the clinical setting. Kumar et. Al (2013) evaluated 34 patients undergoing cardiac surgery with conventional diastolic and tissue Doppler parameters using intraoperative TEE with concurrent Pulmonary artery catheter monitoring before and after cardiopulmonary bypass (CPB), and found that at both pre- and post- CPB, there was no significant correlation between lateral, septal and mean mitral e/e’ ratio obtained by TEE and pulmonary capillary wedge pressure and assumed that intraoperative TEE was unable to accurately predict the left ventricular filling pressure (LVFP) in patients undergoing cardiac surgery and that pulmonary artery catheter may continue to be the gold standard in the assessment of LVFP for the patient population (17).

Mario Previtali et al. (2012) carried out Echo-Doppler examination and left heart catheterization in 100 consecutive patients to assess the correlation between echo-Doppler parameters and the LVDP and found that mitral e/a ratio showed the best correlation with a pre-left ventricular diastolic pressure (LVDP) and left ventricular end diastolic pressure (LVEDP), whereas septal and mean mitral e/e’ ratio were significantly correlated with a pre-LVDP and not with LVEDP in patients without heart failure, and assumed that mitral e/e’ ratio is of limited clinical value in patients without heart failure (18).

Isabelle Michaux et al. (2006) studied the correlation between tricuspid e/e’ ratio and right atrial pressure (RAP) measured by TEE in 44 anesthetized, paralyzed, and mechanically ventilated patients. Linear regression did not indicate a correlation between e/e’ ratio and RAP or between e/e’ ratio and the right or left ventricular end-diastolic area index (19).

One limitation in our study is the inconsistent ability to obtain good Doppler alignment with the tricuspid annulus which makes it impossible to obtain an accurate reading in five cases out of forty. We tried to overcome this by taking repeated measurements. We considered the higher reading to be the more accurate one.

## Conclusion

This study has demonstrated that RV E/e’ positively correlates with right atrial pressure, Systolic pulmonary artery pressure and negatively correlates with TAPSE which makes it a potentially useful index for assessing RV systolic function in the operative setting. More studies are recommended to test its sensitivity and specificity, and whether other factors, such as mechanical ventilation and anaesthesia can affect the measurements.

**Acknowledgment and Author Contributions:** Abdlaziz I: Consenting, measurements and clinical management, Data collection and writing the manuscript. Ashmawi H, Idris D and Hafez H: Supervising and sharing in data collection and revising the manuscript.

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## NEW-ONSET ATRIAL FIBRILLATION FOLLOWING CARDIAC SURGERY

Kostadinovska B<sup>1</sup>, Nikolic A<sup>1</sup>, Slavevski D<sup>1</sup>, Stefanovski I<sup>1</sup>, Bislimovski D<sup>1</sup>

<sup>1</sup> Acibadem Sistina Hospital Skopje, R. North Macedonia

### ABSTRACT

**Background:** Postoperative atrial fibrillation (POAF) following cardiac surgery remains common event in perioperative cardiac surgery, having great clinical and economic implications. It complicates approximately 20-60% of all cardiac surgical procedures and is associated with an increased periprocedural morbidity and mortality, prolonged hospital stay, increased costs, and worse long-term survival. This review seeks to provide evidence-based data of the pathophysiology, clinical risk factors, prophylaxis, treatment modalities and the clinical course.

**Methods:** A literature review has been performed using mainly PubMed to overview the current practice with available evidence. The Google Scholar search engine was also included.

**Results:** AF is the most common arrhythmia after cardiac surgery and occurs in approximately 20–50% of the patients depending on the type of surgery. There are several mechanisms triggering POAF such as: the systemic inflammatory reaction caused by use of CPB, local inflammation caused by surgical incision, sympathetic activation after cardiac surgery, the pre-existence of a cardiac substrate for AF, non-cardiovascular risk factors, and procedure associated: CPB and aortic cross-clamp duration. Pre-, peri- and post-operative prophylaxis with a selection of right antiarrhythmic medication lead to decreased occurrence and earlier restoration of regular rhythm.

**Conclusion:** Some of the mechanisms involved in the genesis of POAF are known, but they are still not fully understood. Knowledge of these mechanisms permits the use of efficient measures to reduce the incidence of this arrhythmia. Supported by studies with high level of evidence, there are recommendations supporting the use of prophylactic and treatment options, but the optimal prophylactic and treatment measures still remain unclear.

**Key Words:** Cardiac surgery, postoperative atrial fibrillation, prophylaxis, treatment.

### Introduction

AF is the most common arrhythmia after cardiac surgery and occurs in approximately 20–50% of the patients depending on the type of surgery, specifically in 30–40% of the patients post coronary artery bypass graft (CABG), up to 60–70% of the patients with combined CABG and valve surgery, and in 11–24% of the patients after cardiac transplantation (1, 2). Sixty percents of the episodes occur on day 2–3 of the post-operative period and 57% of the patients experience only one episode (2, 20). The majority of the post-op AF convert to sinus rhythm in the first 24–48 hours and if it takes longer than 48 hours, there is an increased risk of stroke. AF in post-cardiac surgery may cause HF and hemodynamic instability, and may prolong hospital stay and increase the costs. Postoperative AF affects both early and late mortality after isolated CABG surgery. The most of complications are related to stroke, therefore careful postoperative surveillance for antithrombotic prophylaxis is warranted. Post pericardiotomy and inflammation play significant role in the pathophysiology of post-cardiac surgery AF (2).

**Picture 1.** A summary of the risk factors for preoperative, intraoperative and postoperative AF.

Reproduced from Mohammad S, A. John Camm. Management of atrial fibrillation. A practical approach. Oxford University Press 2015

A summary of the risk factors for preoperative, intraoperative, and postoperative AF		
Preoperative	Intraoperative	Postoperative
Age, male gender, race	Damage to the atrium	Volume overload
Previous history of AF	Atrial ischemia/infarction	Increased after load
HF	Acute volume change	Hypertension/hypotension
Previous cardiac surgery	Insertion of a ventilator tube	Inflammation
Concomitant valve surgery	Venous cannulation	Atrial extrasystole
LV dysfunction	Electrolyte imbalance	Post-pericardiotomy syndrome
Renal dysfunction	Systolic BP > 180 mm or < 80 mm	Autonomic nervous system imbalance
Hypertension	Inadequate cardiac protection during bypass	Electrolyte imbalance
Diabetes	Hyperadrenergic state	Post-op anaemia
Valvular heart disease	Right coronary artery surgery, etc.	Longer duration of mechanical ventilation
Obesity/metabolic syndrome	Atriotomy	Pericarditis/pericardial effusion
High BNP levels		
Stroke		
Previous MI		
COPD		
LA size and volume		
Pre-op $\beta$ -blockers		
Withdrawal of $\beta$ -blockers		
P wave duration > 116 ms		

BNP = b-type natriuretic peptide; BP = blood pressure; COPD = chronic obstructive pulmonary disease; HF = heart failure; LA = left atrium; LV = left ventricular; MI = myocardial infarction.

### Aim of This Review

This review seeks to provide evidence-based data of the pathophysiology, clinical risk factors, prophylaxis, treatment modalities and the clinical course. It is highly important for each cardiac surgery center to have a well-developed strategy and protocol for prophylaxis and treatment of atrial fibrillation related to the cardiac surgery. This should improve the overall outcome, reduce the post-operative complications and reduce healthcare costs.

### Methods

In this review article, a comprehensive literature review was performed using PubMed and Google Scholar search engine. We used the key words 'postoperative atrial fibrillation', 'prophylaxis of atrial fibrillation following cardiac surgery', 'pathophysiology', 'guidelines', 'treatment of atrial fibrillation following cardiac surgery'. The most relevant and recent POAF literature and current clinical guidelines were examined and summarized.

## PATHOGENESIS OF POAF

### Local and Systemic Inflammation and Oxidative Stress

The similarity between the time course of AF occurrence after cardiac surgery and the activation of the complement system with the release of pro-inflammatory cytokines, suggests an inflammatory component in the mechanism triggering POAF. Complement activation during cardiac surgery with cardiopulmonary bypass (CPB) occurs in two steps. The first phase occurs during CPB, resulting from interaction between the blood and the surface of the extracorporeal circuit, and it is mediated via the 'alternative pathway' involving tumor necrosis factor  $\alpha$ . The second phase acts via the 'classical pathway' which is initiated by protamine, usually administered after CPB. Interestingly, fever and POAF do not occur before the first post-operative day and thus coincide with the second phase rather than with the first one. Their time course corresponds to changes in activity of markers indicating complement activation and inflammation, such as C-reactive protein (CRP), complement-CRP complexes, interleukin-2 and interleukin-6 (9, 17).

Also, more pronounced increase in the post-operative white blood cells count as a marker of inflammatory response independently, predicts the development of post-operative AF in some studies, but not in the others. Furthermore, patients developing POAF have up-regulated monocyte activation and higher monocyte and neutrophil levels post-CPB (6, 17).

Besides the systemic inflammatory reaction caused by use of CPB, also local inflammation caused by surgical incision contributes to the occurrence of POAF. It is known that the degree of atrial inflammation increases with the invasiveness of surgery, but even after pericardiotomy alone, the atrium becomes mildly inflamed. This transient sterile pericarditis, which is part of the healing process, might help to explain the temporal occurrence of POAF. Comparison of AF incidence after off-pump and on-pump surgery facilitates to distinguish the importance of

the systemic inflammation from that of surgical incision and manipulation. As such, off-pump CABG (OPCAB) is believed to elicit less systemic inflammation than on-pump surgery because of reduced cytokine responses and less myocardial injury (17).

Finally, it is known that chronic inflammation in patients can cause atrial structural remodeling (4, 6). C-reactive protein is associated to and predicts patients at risk of developing future non-surgical AF. This chronic inflammation might also predispose to the occurrence of POAF (9, 17).

Oxidative stress occurs from an imbalance between pro-oxidants and antioxidants, in favor of pro-oxidants. The use of CPB in cardiac surgery involves controlled ischemia followed by the reperfusion of the heart. During reperfusion, increased production of reactive oxygen species takes place, leading to myocardial stunning, tissue damage, and cell death (6, 17, 20).

### Sympathetic Activation

In the heart, sympathetic stimulation is mediated by  $\beta$ -adrenoreceptors and it leads to an increase in the heart rate and contractile force, but also it leads to enhanced excitability and automaticity. Several findings support the role for sympathetic activation in the pathogenesis of atrial arrhythmias after cardiac surgery. Advanced age, the most important risk factor for POAF, is associated to increasing circulating norepinephrine levels. Patients who develop POAF also have significantly elevated norepinephrine levels post-operatively, compared to the patients without POAF. However, controversy remains if this sympathetic activation is accompanied by either increased activity or loss of vagal tone. Finally, sympathetic activation has been reported to shorten atrial refractoriness nonuniformly, thereby favoring the perpetuation of the arrhythmia. On the other hand, there is a slight discrepancy between the peak of sympathetic activation, which occurs within 24 h postoperatively, and the onset of POAF, mostly developing between 48 and 72 h after surgery (1, 17).

### Presence of a Substrate

Besides AF promotion by acute, surgery-induced factors, also the pre-existence of a substrate for AF can predispose to onset of the arrhythmia in the post-operative setting (6, 17).

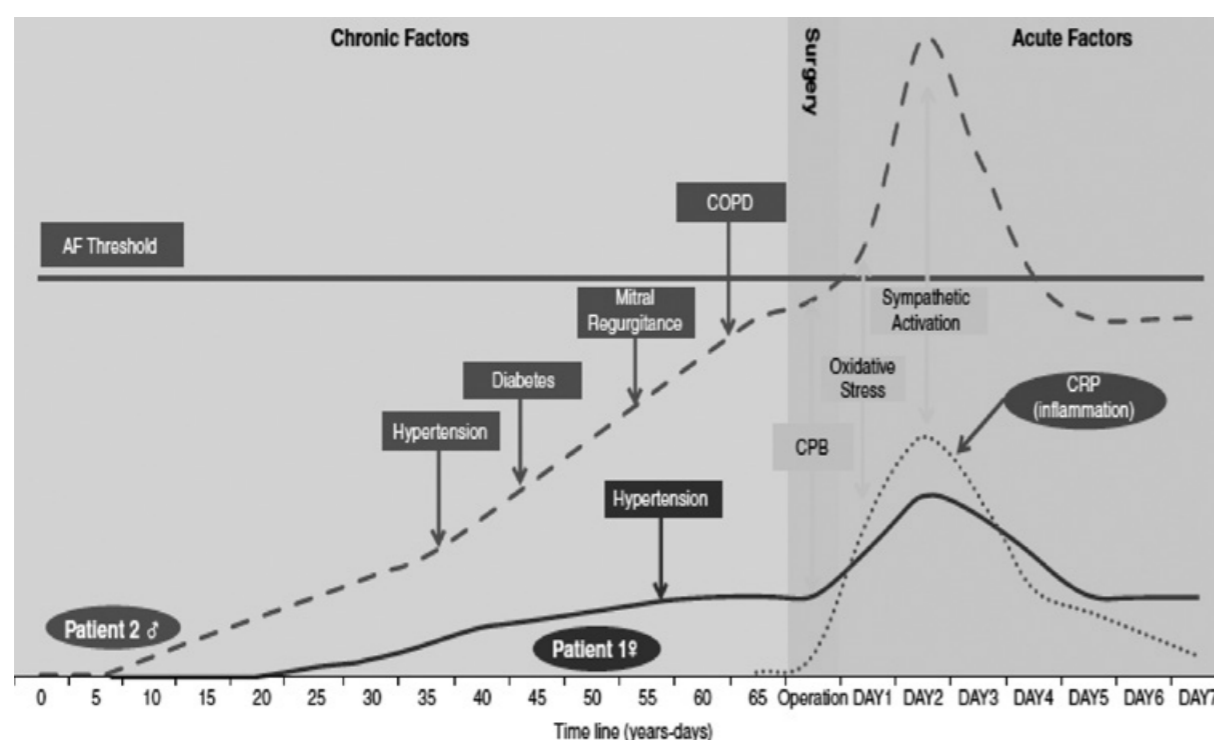
Development of such AF substrate can involve ion channel alterations resulting in shortening and/or enhanced dispersion of atrial refractoriness and heterogeneities in conduction due to interstitial alterations like, for example, accumulation of collagen fibers, inflammatory infiltration or amyloidosis (4, 17).

Ageing is an important risk factor for POAF and slowing of conduction is known to occur as atria structurally remodel with age. Progressive electrical uncoupling of the side-to-side connections between parallel-orientated atrial fibers occurs in atrial muscle with advancing age. This uncoupling results in a decrease of transverse conduction and enhances anisotropy of the conduction velocity. Such an alteration in conduction is often associated with the presence of the

extensive collagenous septa and favors reentry. Left atrial fibrosis is more pronounced in patients undergoing mitral valve surgery compared with patients undergoing CABG, independently of the underlying heart rhythm. It appears reasonable to assume that the higher AF incidence after mitral valve surgery is due to these structural alterations (1, 6, 17, 20).

Association between chronic obstructive pulmonary disease (COPD) and new onset AF is still under discussion. The pathogenesis of AF in patients with COPD is unclear, but pulmonary hypertension, inflammation, hypoxia, acidosis, and right atrial and ventricular dilatation might contribute to the formation of a substrate for AF in these patients (16, 17).

**Picture 2.** Time course of substrate development and factors related with surgery in the onset of atrial fibrillation.



Also the figure indicates the importance of pre-existing factors in the occurrence of atrial fibrillation following the cardiac surgery. Reproduced from Bart Maesen et al. Post-operative atrial fibrillation: a maze of mechanisms. *Europace* (2012) 14, 159–174 doi:10.1093/europace/eur208.

Non-cardiovascular risk factors for POAF include: male gender, Caucasian race, chronic obstructive pulmonary disease, high cholesterol, hyperthyroidism, chronic kidney disease, diabetes, obesity and greater body surface area. Individuals with a high body surface area (around 2.0 m<sup>2</sup>) often have larger atria and abnormal intrathoracic pressure, which may alter atrial electrophysiological properties and increase susceptibility to POAF. POAF has also been associated with decreased mitochondrial function in patients with diabetes and metabolic syndrome (20).

CPB and aortic cross-clamp duration have consistently been associated with POAF, and some studies have shown that reducing CPB and cross-clamp time may reduce POAF. Off pump cardiac surgery (primarily off-pump CABG and transcatheter approaches) has been shown to

yield a lower incidence of POAF in the most of the large studies. However, only about 20% of CABGs are currently performed off-pump, and the most of the surgeons do not routinely perform this procedure. Intra-aortic balloon pump usage, prolonged ventilation time, return to the ICU, cardiac tamponade and reoperation for bleeding are also predictors of POAF. Retained blood in the chest cavity can lead to cardiac tamponade or can form clots, which undergo inflammatory changes that amplify local and systemic inflammation (17).

## PREOPERATIVE POAF PROPHYLAXIS

### β-Blockers

In a recent meta-analysis, beta-blockers in general were found to significantly reduce the risk of POAF from 32.8% in controls to 20.0. Indeed, beta-blockers are the most widely used prophylactic medications for patients undergoing cardiac surgery, and current guidelines from Europe and the US, suggest beta-blocker administration for at least 24 hours prior to surgery as a Class I recommendation for patients undergoing CABG, especially for those who have an ejection fraction greater than 30%. Importantly, preoperatively instituted beta-blocker treatment is more effective than de novo beta-blocker treatment early after the operation, and patients that cease beta-blocker use prior to surgery, have more than a twofold increase in the risk of POAF compared to those who remain on treatment. This may be due to the synergistic effect of the rebound phenomenon of increased cardiac excitability and automaticity, as well as the generally higher postoperative sympathetic tone. However, caution is warranted, as beta-blockers carry a risk of bradycardia, hypotension, bronchospasm, and heart failure exacerbation. Perioperative withdrawal of beta-blocker or angiotensin-converting enzyme (ACE) inhibitor therapy has been associated with the increased risk of POAF (1, 4, 6, 16, 18, 20).

### Other Antiarrhythmic Drugs

Class III AADs such as amiodarone (the most widely used AAD), ibutilide, dofetilide and sotalol (which also has β-blocking effects) have also been widely used prophylactically in the preoperative period. Prophylactic amiodarone and sotalol are currently listed as Class II recommendations for POAF prevention. Studies have demonstrated that preoperative prophylactic oral amiodarone regimens (10 mg/kg started 6 days preoperatively in one large study, 600 mg/day for 7 days preoperatively in another) significantly decreased the incidence of the postoperative atrial arrhythmias, stroke and hospital length of stay compared to placebo without any adverse complications other than occasional bradycardia. Administration of sotalol 24–48 h before surgery has also been shown to significantly reduce the risk of POAF, but sotalol prophylaxis carries a higher rate of adverse side effects, such as bradycardia and ventricular arrhythmias. Preoperative prophylactic administration of Class I AADs, including procainamide and propafenone, are not recommended due to their pro-arrhythmogenic properties (1, 6, 20).

### **Corticosteroids**

Corticosteroids decrease the heterogeneity of atrial conduction and reduce inflammation following cardiac surgery, and studies have shown that preoperative prophylactic corticosteroids reduced POAF incidence without increased rate of postoperative infection. The most effective dosage and administration method of preoperative prophylactic corticosteroids remains unclear, however. One meta-analysis determined that doses of less than 1000mg hydrocortisone administered 24–72 h preoperatively, significantly reduced the incidence of POAF, while another meta-analysis concluded that intermediate doses (4 days of 100mg or one dose of 200–1000mg of hydrocortisone, or one dose of 50–210mg of dexamethasone) were more effective than lower (up to 8mg) or higher (236–2850mg) doses. Since corticosteroids carry the risk of hyperglycemia, immunosuppression, impaired wound healing, and increased gastrointestinal complications, they pose extra risk for certain patients and have not been widely adopted. [10,1,6,20]

### **Statins**

Statins also reduce inflammation and oxidative stress following cardiac surgery, and early studies showed that preoperative statins significantly reduced POAF incidence. Dosage varied between these studies, from 20 to 80mg, as did the time of administration, from 4 weeks preoperatively to the evening before. More recent studies have shown conflicting data, however, and recommendations for preoperative statin prophylaxis cannot be made at present (4, 10, 20).

### **Sodium Channel Blockers (quinidine, lidocaine, flecainide)**

These drugs block the Na<sup>+</sup> channels, thereby reducing automaticity. However, they may initiate arrhythmia by exaggerating electrophysiological abnormalities evoked by ectopic beats, and their prophylactic use in surgical patients has not been thoroughly investigated (1, 10, 11).

### **Calcium Channel Blockers (verapamil and diltiazem)**

Medications from this class reduce cardiac contraction (negative inotropic effect) and by acting on the conduction tissue, they slow down the conduction of electrical activity within the heart (negative chronotropic effect) by calcium channel blockade. These drugs have a minor effect in minimizing the risk of POAF after cardiothoracic surgery, but they increase the risk of bradycardia and hypotension. Of note, studies even indicate that these drugs might increase the risk of POAF, as they reduce the conduction at the sinoatrial node and atrioventricular node (1, 4, 10, 16).

### **Digoxin, Magnesium, and Other Cardiac Drugs**

Digoxin enhances the intracellular calcium concentration, prolonging phase 0 and phase 4 of the cardiac action potential and thereby reducing the heart rate. Digoxin also enhances vagal activity, and so prolongs the depolarization of pacemaker cells in the AV node causing a reduction in the heart rate. By reducing the heart rate, the left ventricle has an increased filling time

that can increase cardiac output, but available evidence does not support the use of digoxin, thiazolidinediones, or triiodothyronine in the prevention of POAF. Although there are some studies that suggest that perioperative administration of magnesium can prevent POAF, this remains controversial since studies are small and the design varies among the different studies. Potassium supplementation has not been shown to influence the incidence of POAF. Magnesium may inhibit substrate formation and the development of re-entrant circuits within the atria and reported adverse effects are few (10, 16, 20).

### **Renin-angiotensin Inhibition (ACE-inhibitors, angiotensin II receptor blockers & aldosterone)**

Aldosterone, a mineralocorticoid, is a steroid hormone produced by the zona glomerulosa of the adrenal cortex in the adrenal gland. It is a part of the renin-angiotensin-aldosterone system that modulates the release of angiotensin. The direct effects of angiotensin blockade on the structural and electrical properties of the atria, as well as the indirect influence of improved control of heart failure and hypertension, are considered to mediate a potential risk reduction for the development of POAF. Finally, a risk score developed in multiple centers for cardiac surgery patients indicates that withdrawal of ACE/ARB had a significant association with increased risk for POAF (1, 10).

### **Anti-oxidative Stress Drugs (N-acetylcysteine, ascorbate, nitric oxide gas)**

Several drugs, including N-acetylcysteine, ascorbate, and nitric oxide gas have been suggested to reduce the risk of POAF, although larger studies are required to make recommendations. In smaller studies N-acetylcysteine has shown promising abilities to reduce the risk of POAF and all-cause mortality after cardiac surgery, whereas in-hospital length of stay was unaffected (1, 5, 10, 16).

### **Colchicine**

Colchicine also has potent anti-inflammatory properties. Gastrointestinal intolerance was the main adverse effect. There is not conclusive evidence to support efficacy as primary prevention. It is not used widely for this purpose (1, 7).

In conclusion,  $\beta$ -blockers should routinely be used as the first choice for the prophylaxis of AF in all patients undergoing cardiac surgery, unless otherwise contraindicated (Grade A recommendation based on level 1a studies).

Sotalol may be more effective than standard  $\beta$ -blockers for the prevention of AF without causing an excess of side effects (Grade A recommendation based on level 1b studies). Amiodarone should be used for prophylaxis of AF in all patients undergoing cardiac surgery in which  $\beta$ -blocker therapy is not possible (Grade A recommendation based on level 1a and 1b studies). In high-risk patients receiving  $\beta$ -blocker therapy for prophylaxis of AF, amiodarone may also be used as additional prophylaxis with an acceptably low incidence of complications. These patients should be protected from the complications of bradycardia with temporary pacing wires being placed intra-operatively (Grade A recommendation based on level 1b studies) (16).



## INTRAOPERATIVE POAF PROPHYLAXIS

**Posterior pericardiotomy.** A posterior pericardiotomy allows pericardial fluid to drain out of the pericardial space, thus decreasing the accumulation of pericardial effusions, which may be a trigger for atrial fibrillation and supraventricular tachyarrhythmias (1, 5, 10, 20).

**Epicardial Fat Pad Manipulations.** The autonomic nervous system may contribute to POAF susceptibility, as atrial tissue receives extensive cholinergic innervation, and an enhanced vagal tone results in decreased atrial refractoriness. Vagal postganglionic neurons are located in the distinct anatomic fat pads distributed around the heart, including the anterior epicardial fat pad, and interventions targeting these neurons were hypothesized to have an effect on POAF. To date, these interventions are not referenced for POAF prophylaxis in any guidelines (1, 10, 20).

**Off-pump Coronary Artery Bypass Grafting.** The inflammatory response to cardiopulmonary bypass (CPB) has been identified as a potential contributor to POAF. Therefore off-pump CABG, which has been found to have a decreased inflammatory response, could in theory decrease POAF. However, there is little evidence that off-pump CABG decreases POAF incidence when compared to on-pump CABG (1, 10, 17).

**LAA (Left atrial appendage) exclusion** has emerged as a target for prophylactic stroke prevention and an alternative to long-term anticoagulation therapy. Large studies are ongoing to evaluate whether LAA exclusion is protective against stroke in the long-term, but recommendation of this technique for a possible short-term advantage cannot be made at this time (4, 10, 20).

## POSTOPERATIVE POAF PROPHYLAXIS

### Medications

$\beta$ -Blockers are the most common medications given for POAF prevention following surgery. Prescription of  $\beta$ -blockers following cardiac surgery remains a Class I recommendation and it is performed in nearly 82% of the cases (1, 5, 10, 20).

When the use of  $\beta$ -blockers is contraindicated, such as in patients with poorly controlled asthma or heart failure, postoperative administration of amiodarone is considered to be the second choice for POAF prevention. A recent Cochrane review of 118 studies reported that postoperative administration of amiodarone significantly reduced the incidence of POAF compared to control.

The efficacy of postoperative ACE inhibitors in POAF prevention is questionable; some studies have shown that postoperative ACE inhibitors decreased POAF incidence, while the others showed no difference or an increase in comorbidities, such as recurrent angina (1, 10, 20, 23).

### Atrial Pacing

The use of prophylactic overdrive atrial pacing after cardiac surgery improves the intra-atrial conduction and prevents triggering events, such as premature atrial contractions or atrial refractoriness. Various studies have reported mixed results regarding the effectiveness of single- or dual-chamber atrial pacing following cardiac surgery on POAF incidence (1, 4, 5, 10, 20).

## Electrolyte Supplementation and Repletion

Current clinical practice often includes intraoperative and postoperative repletion of magnesium and potassium, although their effects remain controversial. Additionally, intraoperative and postoperative electrolyte supplementation has been proposed as a means of POAF prophylaxis, but this has also not been definitively shown to prevent POAF (1, 10, 20, 23).

## Treatment

POAF may resolve spontaneously within minutes or hours, but persistent episodes of AF, especially those provoking hemodynamic instability, require clinical intervention. Importantly, the treatment includes general measures, such as optimization of electrolyte abnormalities or fluid balance, treatment of infections, and drainage of pleural and pericardial cavities (1, 6, 10).

There are two general approaches for treatment of POAF: rate control and rhythm control (4, 20). Rate control focuses on slowing the heart rate and includes the use of  $\beta$ -blockers or calcium channel blockers. Rhythm control focuses on converting the arrhythmia into sinus rhythm by using Class I or III AADs or direct-current cardioversion for unstable patients or those with persistent episodes of POAF. A recent prospective clinical study, comparing rate versus rhythm control, found that neither treatment strategy offered a significant clinical benefit over the other in terms of postoperative mortality, bleeding, thromboembolic events, length of stay, or freedom from AF at 60 days (4, 10, 20).

The control of ventricular response during AF can be performed with various drugs, including digitalis,  $\beta$ -blockers, and calcium channel blockers. However, the control of response during this period, characterized by increased adrenergic stress, can be particularly difficult.  $\beta$ -blockers are the first-choice medications in the postoperative care after cardiac surgery, especially in the presence of ischemic heart disease, unless there are contraindications. Importantly, they may be poorly tolerated or contraindicated in the presence of bronchial asthma, decompensated heart failure, and atrioventricular (AV) conduction disorders. Alternatively, calcium channel blockers may be used, except in the presence of AV conduction disorder. Digoxin is less effective because it lacks action on adrenergic tone superimposing the vagotonic effects of the drug on the AV node, but it may be used in the presence of congestive heart failure. In hemodynamically unstable patients, ultrashort-acting  $\beta$ -blockers, such as esmolol and landiolol, may provide better relief. Small-scale trials examining the effectiveness of landiolol have shown promising results, but further studies are warranted (1, 6, 10, 20).

Class III AADs (potassium channel blockers) such as amiodarone may also be used to convert patients to sinus rhythm, but they are associated with bradycardia, hypotension and QT interval prolongation. These agents are a Class II recommendation for POAF management and may be used independently or in conjunction with  $\beta$ -blockers, or as the first-line treatment in patients with hypotension, heart failure, or LV dysfunction. Discharge on any Class III AAD has been associated with a reduction in all-cause postoperative mortality, but long-term Class

III AAD use has been linked with prolongation of atrial and ventricular refractory periods. The 2014 American Association for Thoracic Surgery (AATS) guidelines state as a Class II recommendation that AAD usage for patients discharged in sinus rhythm should be continued for 4 weeks after the last episode of POAF or until the first postoperative visit (2–6 weeks after discharge), while patients discharged in AF should continue AAD usage for 4 weeks following the first postoperative visit without POAF recurrence. The 2010 Canadian Cardiovascular Society guidelines state that treatment may be discontinued between 6 and 12 weeks after restoration of sinus rhythm (1, 10, 20, 23).

The effectiveness of Class I AADs (sodium channel blockers), such as procainamide, flecainide and propafenone, in POAF treatment is unclear, but these medications carry significant risk of pro-arrhythmic side effects and are therefore not recommended for the treatment of POAF.

Electrical cardioversion is often an effective way of establishing cardioversion, but it is the most commonly used in symptomatic patients with hemodynamic instability, acute heart failure, myocardial ischemia, or POAF refractory to medical cardioversion as it necessitates the most often procedural sedation. Electrical cardioversion without anticoagulation is assumed to be safe when performed within 48 hours after development of POAF. Therefore, it can be used in symptomatic or even asymptomatic patients within this timeframe as an alternative to medical conversion, though the risk of a new event of POAF remains high if medical therapy is not instigated. When POAF has been of a longer duration transesophageal echocardiography (TEE) is recommended in order to exclude the presence of a left atrial appendage thrombus prior to the electrical cardioversion. Cardioversion is listed as a Class I recommendation by the AATS and a Class II recommendation by the 2014 AHA/ACC/HRS task-force. If there is a need for repeat cardioversion, concurrent pharmacologic rhythm or rate-control drugs can be considered in order to optimize successful and sustained cardioversion (1, 6, 10, 20).

In the ACC/AHA/HRS practice guidelines, ibutilide is specifically named as a reasonable choice of pharmacological agent for restoring sinus rhythm in AF. It is associated with ventricular arrhythmias including sustained polymorphic ventricular tachycardia, it requires close rhythm monitoring for at least 4 hours after administration, and it is contraindicated in the patients with QT prolongation, hypokalemia, and reduced ejection fraction (10).

#### **Anticoagulants (warfarin)**

Within the first 48 h of POAF, anticoagulation to prevent thromboembolism is a Class I recommendation. However, bleeding risk may outweigh the benefits of anticoagulation in patients with advanced age, uncontrolled hypertension, or a history of bleeding. In such patients, postponing anticoagulation, implementing a rhythm control approach using pharmacological agents, or performing cardioversion without anticoagulation, may be beneficial (1, 3, 10, 20, 23).

Administration of anticoagulants and antithrombotic to patients without contraindications is listed as a Class I recommendation for episodes lasting longer than 48 h. NOAC usage is listed

as a Class II recommendation in patients where warfarin is contraindicated. NOACs are likely more effective than traditional warfarin at preventing stroke and major postoperative bleeding events, they have fewer drug–drug interactions, and have rapid on/off action. The short half-life of NOACs makes strict compliance important to ensure complete thromboembolism. NOACs should not be used in patients with renal impairment (since no reversal agent exists to prevent renal damage if misused), those with a prosthetic heart valve, or those with impaired valve hemodynamics. Low molecular weight heparin may also serve as an alternative to warfarin in patients with high bleeding risk, low platelet counts and those who may require additional invasive procedures after discharge (1, 6, 10, 20).

Anticoagulants and antithrombotics should be continued for a minimum of 4–6 weeks after return to sinus rhythm, but they may be continued for longer depending on the patient's stroke risk. Due to the self-limiting nature of POAF, long-term usage is often not warranted. For patients who may require long-term anticoagulation due to POAF, the AATS recommends cardiology follow-up (1, 20).

#### **Conclusion**

Patients who develop POAF often experience other postoperative complications. The most common associated complications are ventricular arrhythmias, perioperative MI, congestive heart failure, need for permanent pacemaker implantation, acute kidney injury, infection, pneumonia, prolonged mechanical ventilation, increased need for tracheostomy, need for intra-aortic balloon pump (IABP), increased postoperative bleeding, and cardiac tamponade. The most important, the incidence of stroke association with POAF is threefold higher, and 30-day mortality is twofold higher, compared to the patients who don't develop POAF. Furthermore, hospital costs are significantly higher, mostly due to the fact that the hospital stay in POAF patients is increased by two to four days (1).

It is unlikely that there is a single unifying mechanism for development of this arrhythmia, and current studies point to the high likelihood of multiple disparate pathways leading to the common outcome of POAF (17).

The optimal preventive measures as well as optimal short- and long-term treatment options also remain unclear. Further well designed prospective and retrospective studies focusing on pathophysiology, prevention, and therapy in experimental models and in sufficiently large patient populations are warranted (1, 10, 20).

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## RESPIRATORY FAILURE IN A CHILD WITH ASSOCIATED CONGENITAL HEART DEFECT

Stojanovic V<sup>1</sup>, Chadikovski V<sup>1</sup>, Radoeshki A<sup>1</sup>, Krmzova M<sup>1</sup>, Trpkovska V<sup>1</sup>, Kamnar V<sup>2</sup>

<sup>1</sup> Acibadem Sistina Hospital, Skopje, Macedonia

<sup>2</sup> University Clinic for Orthopedic Diseases, Skopje, Macedonia

### ABSTRACT

The following report presents a case of an almost two-months-old infant suffering from a huge persistent ductus arteriosus, right kidney hydronephrosis and crossed left ectopic kidney. Persistent ductus arteriosus in this case was diagnosed later and it was ligated at two months of age. This case study aims to emphasize the association of congenital heart defects (CHD) accompanied by other systems' anomalies, especially in patients with pronounced respiratory symptomatology.

**Key Words:** congenital heart defect, respiratory failure.

### Introduction

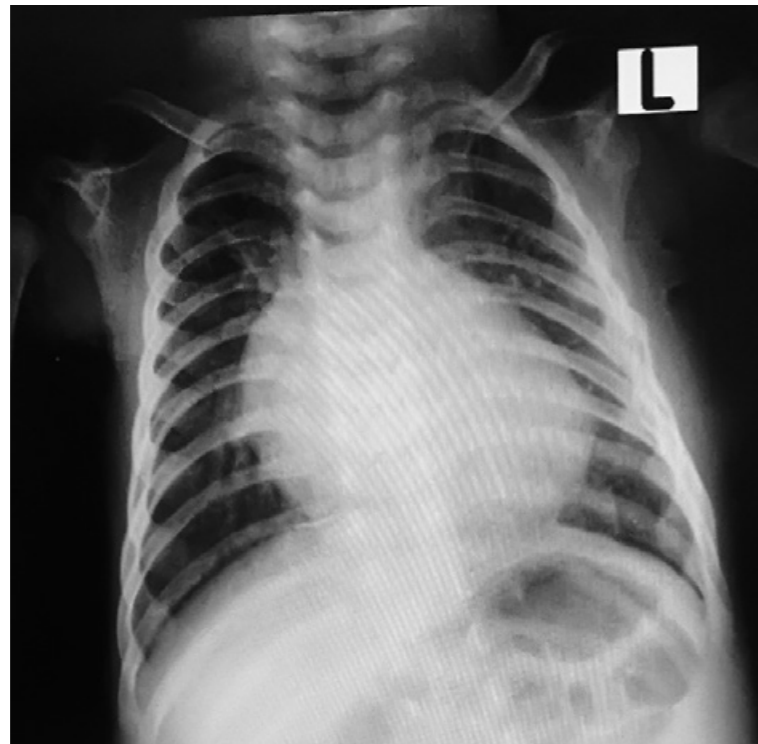
Crossed ectopic kidney is a rare anomaly with its real incidence being unknown since some patients have no symptoms. The incidence is estimated to be about 1 in 1,000 newborns. There is gender predilection for men in a ratio of 2:1. Left to right ectopia is three times more common, as in the case of our patient. The frequency of hydronephrosis in these patients is about 50%. There is strong association of congenital heart defects with renal and urinary tract anomalies.

### Case Report

Two months old infant was admitted at the Department of Pediatric Cardiac Surgery following its prior treatment at the Pediatric Intensive Care Unit. The patient is a first child from first, spontaneous pregnancy. Born in term, birth weight 3230 grams, APGAR 7/5/7. (Figure 1)



**Figure 4.** (Postoperative AP chest CT) The heart is still enlarged, the right ventricle is smaller. No pleural effusions



## Conclusion

These data indicate a significant association of congenital heart defects with congenital renal and urinary tract abnormalities. Given these results, the authors conclude the importance of thinking in that direction when diagnosing a neonatal patient. Of course, it is very important to rule out or confirm other accompanying congenital abnormalities. Congenital anomalies of the kidney and urinary tract continue to be a group of diseases with different degrees of severity and many of them require a multidisciplinary approach for accurate diagnosis and better treatment. Since many of these congenital anomalies are hereditary, advances in prenatal diagnosis, fetal surgery, combined liver and kidney transplants, as well as targeted therapies have improved the prognosis and quality of life in affected families. The outcome of the child was excellent, it was discharged 10 days after operation. On the control examination 10 days after with good weight gain of 500gr.

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## Discussion

Congenital heart defects are the most common congenital defects, occurring in 1% of live births (1,4). It is important to note that these defects often occur in combination with extra cardiac defects (abnormalities) including renal and urinary tract abnormalities (CAKUT). Statistically, renal and urinary tract abnormalities are associated to 23% of congenital heart defects. These statistics suggest an overlap of genetic etiology for CHD and CAKUT. Specific genetic factors, environmental influences on fetal development, and medications during pregnancy may form the underlying cause of concurrent CAKUT in CHD (4). It is important to know the prevalence, types of maternal risk factors and the natural history of CAKUT associated with CHD. There is very small number of studies who addressed this topic.

Great number of pediatric patients with congenital heart defects from Children's Hospital of Pittsburgh have been also examined. Similar statistical incidence of CAKUT and cystic renal diseases has been present in these children as in laboratory mice (1). An epidemiological study in Atlanta on a sample of 8,000 CHD patients has suggested an incidence of renal abnormalities of 23%.

## ULTRASONOGRAPHIC ENDOMETRIAL THICKNESS AS A PREDICTOR OF THE RISK OF ENDOMETRIAL CANCER IN PATIENTS WITH POSTMENOPAUSAL BLEEDING

Tanturovski M<sup>1</sup>, Aluloski I<sup>1</sup>, Kochoski G<sup>1</sup>, Spasova R<sup>1</sup>, Karadjova D<sup>1</sup>, Dimitrovski S<sup>1</sup>

<sup>1</sup> University Clinic of Gynecology and Obstetrics, University "Ss. Cyril and Methodius", Skopje, Republic of North Macedonia

### ABSTRACT

**Objective:** to determine the diagnostic performance of endometrial thickness measured by transvaginal sonography in diagnosing endometrial cancer in patients presenting with postmenopausal bleeding.

**Patients and Methods:** The databases of the Department of Gynecological Oncology at the University Clinic of Gynecology and Obstetrics in Skopje, in the period January – December 2015 were searched in order to identify patients that underwent endometrial sampling due to newly-diagnosed postmenopausal bleeding.

**Results:** A total of 158 patient records that met the criteria were identified. The prevalence of endometrial cancer was 15.2%. Endometrial thickness was a statistically significant independent predictor of the presence of endometrial cancer and atypical endometrial hyperplasia (OR 1.19 95% CI 1.09-1.29 for each 1mm increase in thickness,  $p < 0.001$ ). The ROC curve analysis in our study had an AUC of 0.83 ( $p < 0.001$ ) and identified a cut-off level for endometrial thickness of 8mm which was associated to a sensitivity of 88.9%, specificity of 65.6%, PPV of 34.8% and NPV of 96.6% for the detection of endometrial cancer. Using a cut-off for endometrial thickness of  $\leq 3$ mm achieved 100% sensitivity.

**Conclusion:** None of the analyzed cut-off points for endometrial thickness achieved optimal diagnostic accuracy, as all cut-off values associated to sensitivity rates above 95% had false positive rates of over 60%. Nevertheless, an endometrial thickness cut-off of 3mm, due to the associated high sensitivity, can safely be used to identify women with postmenopausal bleeding who are highly unlikely to harbor endometrial cancer and that can forego initial endometrial sampling.

**Key Words:** Endometrial cancer, endometrial thickness, transvaginal ultrasound.

### Background

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world (1, 2). It is estimated that 320000 new cases are diagnosed annually, accounting for up to 6% of all newly diagnosed malignant neoplasms. In the Republic of North Macedonia, endometrial cancer is the second most common malignant neoplasm in women (after breast cancer), with an estimated 400 new patients diagnosed annually, and a corresponding age-standardized incidence rate of 24.3 per 100000 women (1).

The hallmark symptom of endometrial cancer is postmenopausal bleeding (PMB), as over 90% of menopausal patients with endometrial cancer present with abnormal uterine bleeding (3). In spite of that, the vast majority of cases of postmenopausal bleeding are associated benign conditions such as atrophy or benign polyps, while EC is the underlying cause of postmenopausal bleeding in only 5-12% of cases, depending on age and associated risk factors (4). Identified clinical risk factors for endometrial cancer, include, but are not limited to age, obesity, nulliparity, use of unopposed estrogen (hormone replacement therapy, HRT), tamoxifen use and specific medical comorbidities such as polycystic ovary syndrome, type 2 diabetes mellitus and hereditary non-polyposis colon cancer (Lynch syndrome).

The clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude or diagnose endometrial carcinoma, the cornerstone of which is histological examination of samples of endometrial tissue. In the Republic of North Macedonia, patients with postmenopausal bleeding usually undergo dilatation and curettage (D&C) with or without hysteroscopy. It should be noted that the clinical risk factors associated to the development of EC also increase the procedure and anesthesia risks during invasive diagnostic procedures. Carrying out ambulatory surgery in patients with severe obesity and/or other comorbidities requires complex anesthesiology management, which is a limiting factor in some patients (5-7). Less invasive alternatives, such as endometrial biopsy, provide a smaller tissue sample and, consequently, are more likely to miss localized endometrial lesions (8).

Transvaginal ultrasound scanning (TVUS) to measure the endometrial thickness (ET) has historically been recommended as a first-line investigation of patients with postmenopausal bleeding (9-11). The rationale behind this is two-fold: ET measurement allows the clinician to identify a group of women with postmenopausal bleeding that do not require invasive diagnostic procedures, as patients who have thin endometrium have a very low likelihood of harboring endometrial neoplasia; furthermore, the scan does not require uterine instrumentation and therefore is not hindered by a stenotic cervical or associated with estrogen deficiency in these patients. Research data from studies designed to tackle the question of the optimal ET cut-off point for referring patients with PMB for endometrial sampling has been heterologous, resulting in different proposed cut-offs from various professional groups. The American College of Obstetricians and Gynecologists (ACOG) recommended a cut-off of  $\leq 4$ mm (9), The Society of Gynecologic Oncology and Society of Obstetricians and Royal College of Obstetricians and Gynecologists of Canada recommend

≤5mm (10), while the Scottish Intercollegiate Guidelines Network recommended different cut-off values for women receiving HRT and women not on HRT (≤5mm and ≤3mm, respectively) (11).

Given that all patients referred to our institution for the evaluation of PMB undergo endometrial sampling by D&C to exclude EC, irrespective of the ET measured by TVUS, we conducted a retrospective analysis to better define the rationale for further invasive diagnostic evaluation of patients presenting with postmenopausal bleeding.

## Objective

The objective of the study was to determine the diagnostic performance of endometrial thickness measured by transvaginal sonography in diagnosing endometrial cancer in patients with postmenopausal bleeding.

## Patients and Methods

This retrospective study was conducted at the Department of Gynecologic Oncology at the University Clinic of Gynecology and Obstetrics, University “Ss Cyril and Methodius”, Skopje, Republic of North Macedonia. We searched the Clinic’s patient registers from January until December 2015 for eligible postmenopausal patients presenting newly referred with a first episode of PMB that were admitted at our outpatient department for endometrial sampling. Exclusion criteria were: (1) incomplete medical records; (2) known history of endometrial hyperplasia/cancer; (3) history of tamoxifen use; (4) incomplete patient records; (5) history of hormone replacement therapy; (6) known history of hereditary non-polyposis colon cancer (HNPCC); (7) inadequate endometrial sample for histopathology. The following data were extracted from the patient records: age at sampling, age at menopause, parity, body mass index (BMI), American Society of Anesthesiologists physical status rating (ASA), history of hypertension and diabetes, endometrial thickness and the histology from the endometrial sampling. Post-menopause was defined as the absence of periods for at least 12 months prior to the sampling. Diabetes and hypertension were documented in patients that were already diagnosed (i.e. no first diagnosis during the admission for ES). The departmental protocol for evaluation was TVUS for ET, followed by endometrial sampling within 14 days from the initial evaluation. All TVUS scans were performed using a standard 3-9Mhz transvaginal transducer by attending physicians staffing the outpatient department. The endometrial thickness measurement was acquired in the mid sagittal plane at the thickest part. All patients underwent D&C, with optional previous hysteroscopic evaluation (at the discretion of the attending) under general anesthesia. All histological samples were evaluated at the Department of histopathology at the University Clinic for Oncology and Radiotherapy, University “Ss. Cyril and Methodius”, Skopje, Republic of North Macedonia.

## Statistical Analysis

The data was anonymized and entered into a database. Standard descriptive statistics were done and data were displayed using frequencies, percent, mean and standard deviation (SD), where

appropriate. Based on the histopathology reports, a binary outcome variable describing the presence of EC was created. For statistical purposes, patients with atypical endometrial hyperplasia (AEH) were included in the EC group, based on the argument that the entities are two phases of the same disease continuum and that there is high rate of underdiagnosed malignancies and/or progression to cancer in patients with atypical endometrial hyperplasia (12, 13). Association between the presence of endometrial malignancy and category variables were checked using Chi-square and Fisher’s exact test, where appropriate. Differences between the continuous variables in regard to the presence of EC were tested using the Mann-Whitney U test. A multi-variation binary logistic regression was carried out to exclude possible confounders and identify statistically significant independent predictors of the presence of EC.

The diagnostic performance of endometrial thickness was evaluated by plotting receiver-operating characteristic (ROC) curves and calculated the area under the curve (AUC). Sensitivity, specificity positive and negative predictive value (PPV and NPV) and Youden’s index of the test were calculated for each ET cut-off point. The point with the highest Youden index was selected as the optimal cut-off in our data. All statistical tests were two-sided, with p values below 0.05 considered statistically significant. The statistical analysis was carried out using the SPSS statistical software package version 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

## Results

We identified total of 158 patients’ records that fitted the inclusion and exclusion criteria. Table 1 summarizes the relevant demographic and clinical patients’ characteristics.

The average patients’ age at the time of sampling was 60.9±8.8 years, ranging from 46-82 years. The mean interval from onset of menopause to endometrial sampling was 10.9±9.1 years (range 1-40 years). The mean BMI was 31.77±7kg/m<sup>2</sup> (range 19.9-63.5kg/m<sup>2</sup>). Eighty-seven patients (55.1%) were obese (BMI ≥30kg/m<sup>2</sup>) and 16 (10.1%) patients were morbidly obese (BMI ≥ 40kg/m<sup>2</sup>). Ninety-nine (62.7%) of patients had hypertension, and 38 (24.1%) suffered from diabetes. Seventeen (10.8%) of patients had metabolic syndrome, defined as obesity (BMI ≥30kg/m<sup>2</sup>) with concomitant hypertension and diabetes. Only 7 (4.4%) of the patients in our series were nulliparous. Six patients (3.8%) were classified as ASA 1, 101 (63.9%) patients were classified as ASA 2 and 51 (31.3%) patients were classified as ASA 3. The patients’ characteristics at baseline are summarized in Table 1.

The average ET, measured with TVUS was 8.5±5.3mm (range 2-37mm) with most of the the patients having ET>4mm (122 patients or 77.2%).

A vast majority of the evaluated patients had benign endometrial lesions (131 patients or 82.9%), and 27 patients (17.1%) had premalignant/malignant endometrial lesions. Of the latter group, 3 patients (11.1%) had atypical endometrial hyperplasia and 24 patients (88.9%) had endometrial cancer. The various histological findings are outlined in detail in Table 2.

The patients in our cohort that had an endometrial malignancy were older compared to patients with no malignancy (average age 66 vs. 59, respectively) and the difference was statistically

significant ( $p=0.001$ ). Endometrial thickness was significantly larger in patients with EC, compared to patients with benign pathology (average ET 13.4 vs. 7.4, respectively,  $p<0.001$ ). We did not observe a statistically significant difference between patients with EC and no malignancy in regard to BMI (mean BMI 31.1 kg/m<sup>2</sup> vs. 31.9 kg/m<sup>2</sup>,  $p=0.58$ ). We did not identify a statistically significant difference between in the distribution of risk factors such as nulliparity ( $p=0.22$ ), hypertension ( $p=0.64$ ) and the presence of metabolic syndrome ( $p=0.46$ ) between patients with EC and patients with no endometrial malignancy. Patients with EC were significantly more likely to have diabetes, compared to the patients with benign histology (51.9% vs. 18.3% of diabetic patients respectively,  $p<0.001$ ). The presence of EC was significantly associated to the ASA score as 51.9% of EC patients were ASA Class 3, compared to 28.2% of patients in the benign histology group ( $p=0.04$ ).

**Table 1.** Summary of the relevant demographic and clinical patients' characteristics

Parameter	Total patients included n=268
Age at sampling (years), mean±SD	60.9±8.8
Interval from menopause to sampling (years), mean±SD	10.9±9.1
BMI (kg/m <sup>2</sup> ), mean±SD	31.77±7
Nulliparity, n (%)	14 (5.2%)
Hypertension, n (%)	99 (62.7%)
Diabetes, n (%)	38 (24.1%)
Metabolic syndrome, n (%)	17 (10.8%)
ASA Score	
1, n (%)	6 (3.8%)
2, n (%)	101 (63.9%)
3, n (%)	51 (32.3%)

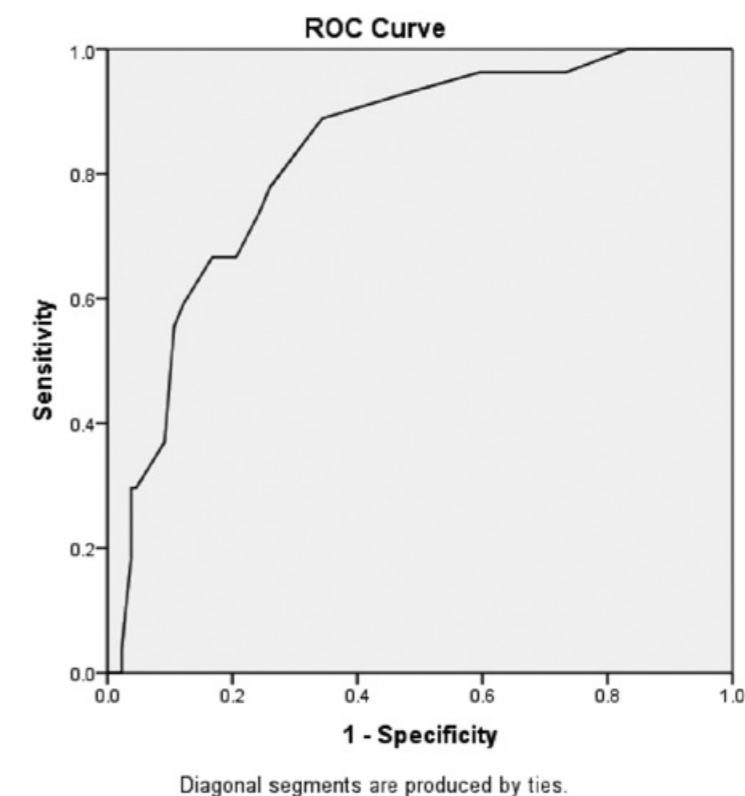
**Table 2.** Distribution of histological diagnoses in the studied population

n (%)	
Atrophic endometrium	84 (53.2%)
Endometrial polyp	27 (17.1%)
Other benign conditions (endometritis, leiomyoma...)	3 (1.9%)
Simple endometrial hyperplasia	13 (8.2%)
Complex endometrial hyperplasia without atypia	4 (2.5%)
Complex endometrial hyperplasia with atypia	3 (1.9%)
Endometrial cancer	24 (15.2%)
Endometroid adenocarcinoma	8 (5.1%)
Mixed serous and mucinous adenocarcinoma	11 (6.7%)
Mucinous adenocarcinoma	3 (1.9%)
Serous adenocarcinoma	1 (0.6%)
Clear cell carcinoma	1 (0.6%)

The multivariate logistic regression revealed ET, measured by TVUS, to be the only independent statistically significant predictor of EC (OR 1.19 95%CI 1.09-1.29 for each 1mm increase in ET,  $p<0.001$ ), while age ( $p=0.13$ ), ASA score ( $p=0.65$ ) and the presence of diabetes ( $p=0.06$ ) lost their significance in the multivariate model.

In order to evaluate the diagnostic performance of endometrial thickness measured by transvaginal sonography for the detection of EC, a ROC curve were plotted (Figure 1). The AUC was 0.83 (95%CI 0.75-0.91,  $p<0.001$ ) indicating moderate accuracy.

**Figure 1.** ROC curve of transvaginal ultrasound measurement of endometrial thickness for the detection of EC in patients with PMB



The results for the diagnostic performance of different cut-off points for endometrial thickness in the detection of EC are summarized in Table 3. The optimal cut-off points for endometrial thickness measured by transvaginal sonography (selected using the Youden index) in our series was 8mm, yielding a sensitivity of 88.9%, specificity of 65.6%, PPV of 34.8% and NPV of 96.6% for the detection of EC. Still, the selected cut-off point correctly classified only 69.6% of the patients (missing 1 case of EC and 2 cases of atypical endometrial hyperplasia) with a false positive rate of 28.5% and did not achieve the clinically required high sensitivity and acceptable specificity rates. Using the  $\leq 3$ mm,  $\leq 4$ mm and  $\leq 5$ mm cut-offs for ET, our data yielded a sensitivity of 100%, 100%, 96.3%, a specificity of 5.3%, 16.8% and 26.7%, with false positive rates of 78.5%, 69% and 60.8%, respectively.



**Table 3.** Diagnostic performance for different cut-offs for endometrial thickness in the detection of EC in patients with PMB

Cut-off point (mm)	Sensitivity	Specificity	PPV	NPV	Youden index	Correctly classified
≥2	100.0%	0.0%	17.1%	100.0%	0.0%	17.1%
≥3	100.0%	5.3%	17.9%	100.0%	5.3%	21.5%
≥4	100.0%	16.8%	19.9%	100.0%	16.8%	31.0%
≥5	96.3%	26.7%	21.3%	97.2%	23.0%	38.6%
≥6	96.3%	40.5%	25.0%	98.1%	36.8%	50.0%
≥7	92.6%	53.4%	29.1%	97.2%	46.0%	60.1%
≥8	88.9%	65.6%	34.8%	96.6%	54.5%	69.6%
≥9	77.8%	74.0%	38.2%	94.2%	51.8%	74.7%
≥10	74.1%	75.6%	38.5%	93.4%	49.6%	75.3%
≥11	66.7%	79.4%	40.0%	92.0%	46.1%	77.2%
≥12	66.7%	83.2%	45.0%	92.4%	49.9%	80.4%
≥13	59.3%	87.8%	50.0%	91.3%	47.0%	82.9%
≥14	55.6%	89.3%	51.7%	90.7%	44.9%	83.5%
≥15	37.0%	90.8%	45.5%	87.5%	27.9%	81.6%
≥16	29.6%	95.4%	57.1%	86.8%	25.0%	84.2%
≥17	29.6%	96.2%	61.5%	86.9%	25.8%	84.8%
≥18	25.9%	96.2%	58.3%	86.3%	22.1%	84.2%
≥19	18.5%	96.2%	50.0%	85.1%	14.7%	82.9%
≥20	18.5%	96.2%	50.0%	85.1%	14.7%	82.9%

## Discussion

The measurement of endometrial thickness by transvaginal ultrasound has long been recommended as the first-line test to triage women presenting with postmenopausal bleeding to endometrial sampling, but consensus as to which ET cut-off should be used to define abnormal is still lacking. Indeed, a precise non-invasive test for discriminating patients with low- and high-risk for development of EC would greatly benefit the clinical practice.

Historical studies have readily demonstrated that increased endometrial thickness is associated to EC in postmenopausal women: in patients with PMB with ET less than 5mm, the risk of EC is low, but the risk rises with increasing ET, especially in patients with ET >20mm (14-16). Increasing ET was an independent, statistically significant predictor of EC in our data, as well (OR 1.19 95%CI 1.09-1.29 for each 1mm increase in ET,  $p < 0.001$ ).

Four large meta-analyses aimed to tackle the question of the optimal cut-off for ET for predicting EC in patients. In the largest meta-analysis published to date, Gupta et al. (17) analyzed data from approximately 9000 patients using 4mm and 5mm cut-offs. The authors demonstrated that an ET cut-off of 3 mm or less would provide a posttest probability of 0.4% for endometrial cancer; a 4-mm threshold, 1.2%; and a 5-mm threshold, 2.3%. Using the pooled estimates

from the studies with the best quality, the authors concluded that a positive test result raised the probability of carcinoma from 14.0% (95% CI 13.3-14.7) to 31.3% (95% CI 26.1-36.3), while a negative test reduced it to 2.5% (95% CI 0.9-6.4).

The meta-analysis published by Smith-Bindman et al., reporting on data from 5892 patients, calculated the overall summary mean weighted estimates of sensitivity and specificity for different thresholds for ET and concluded that using a 5mm threshold for ET would yield a sensitivity of 96% for the detection of EC in women with PMB and that the sensitivity did not vary in women using HRT (18). However, the authors combined published data from different studies into a summary ROC curve, a method which was later criticized by Timmermans et al. on the grounds that it overestimated the sensitivity and specificity of ET measured by TVUS in the detection of EC (19).

In their recent meta-analysis, Timmermans et al. performed a re-analysis of the data using original datasets obtained from authors rather than summary data and were able to acquire data from 2896 cases (259 of which had endometrial cancer) from 13 individual authors, only 2 of which were from the original 90-author group that was reported in the initial publication of Smith-Bindman et al (18, 19). Using this approach and a modified mathematical methodology, Timmermans et al. published that the AUC of their ROC curves varied between 0.82 and 0.84 and concluded that the sensitivity of ET was lower than the one published by Smith-Bindman (18). According to their calculations the sensitivity values for 3-, 4-, and 5-mm cut-offs were 98%, 95%, and 90%, respectively with corresponding false-positive rates of 64.6%, 53%, and 46% (19). It should be noted, however, that at the time of publishing of this meta-analysis, the analyzed cut-off values were already enforced by the primary investigators leading to partial verification of the results, as ES was not performed in patients where ET was below the predefined cut-off.

Tabor et al. analyzed data from 3813 women (330 of which had endometrial cancer) from nine individual studies, publishing detection rates for EC of 63% for a 10% false-positive rate and 96% for a 50% false-positive rate (20). The authors concluded that endometrial thickness measurement in symptomatic women does not reduce the need for invasive diagnostic testing because 4% of the endometrial cancers would still be missed with a false-positive rate as high as 50%.

Wong et al. published a retrospective cohort that included data from 4383 women with postmenopausal bleeding (21). They found that the sensitivity for the detection of endometrial cancer at 3-, 4-, and 5-mm cut-offs were 97%, 94.1%, and 93.5% with an AUC of 0.92. It is worth noting, however, that the study population had a low prevalence of EC (only 3.8% of patients) and patients with non-malignant endometrial lesions had a low mean ET (3.2mm).

A recent retrospective study published in Germany by Schramm et al. reported on data from 254 women with postmenopausal bleeding (22). The authors demonstrated sensitivity of 95.1%, 91.4% and 90.1%, with corresponding false positive rates of 86.1%, 79.2%, and 73.4%, respectively for 3-, 4- and 5mm ET cut-offs, respectively. The authors concluded that there is

no ET cutoff point that provides good diagnostic accuracy and/or reliably excludes the presence of endometrial cancer in patients with PMB.

In our study, the cut-off points for ET of 3, 4 and 5mm showed sensitivity of 100%, 100%, 96.3%, with corresponding false positive rates of 78.5%, 69% and 60.8%, respectively. The most optimal cut-off point was 8mm, correctly classifying 69.6% of the patients and achieving a sensitivity of 88.9% and specificity of 65.6%, well below the standards required for an optimal test. Choosing a lower cut-off point for ET may also not be feasible due to the associated high false positive rate and anecdotal evidence that EC can be diagnosed even in patients with extremely thin endometrium (1mm) (22).

Our study is not free of limitations. First, its retrospective nature being subject to selection bias due to unmeasured confounders. Second, the study was conducted on a gynecologic-oncology department in a tertiary referral center. Although referral for histological diagnosis of patients with postmenopausal bleeding in the Republic of North Macedonia is liberal, it can safely be assumed that not all women with thickened endometrium were referred. Additionally, our cohort comprised of an above-average number (55.1%) of obese patients with comorbidities that were referred to our department they could not be treated safely in a secondary care center, while a good fraction of the patients with PMB with no comorbidities and lower BMI were treated in other outpatient departments. The fact that many of those comorbidities are also risk factors for endometrial cancer might explain the high percentage of diagnosed cancers in our study and could explain why we could not identify a statistically significant association between presence of EC and well known risk factors such as BMI and diabetes. Lastly, we only evaluated the endometrial thickness and disregarded any additional data from the ultrasonography reports, such as specific morphology and/or Doppler evaluation, which could have revealed more information.

## Conclusion

This retrospective cohort analysis found that an increased endometrial thickness, measured by transvaginal sonography, is a significant and independent predictor for the presence of EC in women presenting with postmenopausal bleeding, but it is of modest diagnostic value. None of the analyzed cut-off points for endometrial thickness achieved optimal diagnostic accuracy, as all cut-off values associated to sensitivity rates above 95% had false positive rates of over 60%. Nevertheless, an ET cut-off of 3mm, due to the associated high sensitivity, can safely be used to identify women with postmenopausal bleeding who are highly unlikely to harbor endometrial cancer and that can forego initial endometrial sampling. Still, women with recurrent bleeding symptoms should be advised to re-attend for evaluation.

## Compliance with ethical standards

**Funding:** None.

**Conflict of interest:** The authors report no conflict of interest.

**Contribution to authorship:** TM and AI designed the study and wrote the manuscript; TM, AI, KG, KD, RS, DS, KD were involved in data collection, literature search and reviewing the manuscript. TM performed the data analysis, data interpretation and prepared the tables and figures.

**Ethical approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

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## A CASE OF LARGE WELL DIFFERENTIATED HEPATOCELLULAR CARCINOMA WITH FAVORABLE CLINICAL COURSE

Popova Jovanovska R<sup>1</sup>, Trajkovska M<sup>1</sup>, Genadieva Dimitrova M<sup>1</sup>, Andreevski V<sup>1</sup>, Ramadani A<sup>1</sup>, Deriban Gj<sup>1</sup>

<sup>1</sup> Clinic of Gastroenterohepatology, Faculty of Medicine, University "Saints Cyril and Methodius", Skopje, Republic of North Macedonia

### ABSTRACT

Barcelona Clinic Liver Cancer (BCLC) staging system is the most comprehensive model for prognosis assessment in hepatocellular carcinoma (HCC) patients and it integrates disease stage with treatment recommendations. Disease stage is classified according to the liver function evaluation and factors related to tumor burden including tumor size, number of tumors, vascular invasion and extrahepatic spread. However, in the clinical setting, prognosis in some HCC patients is dependent on the pathological parameters as tumor cell grading, with more favorable clinical course and better survival rate in well differentiated HCC.

A rare (unique) case with a single large tumor measured 9 cm in diameter histologically defined, as well differentiated HCC is presented. Contrast enhanced CT revealed tumor with vague areas of vascularity and necrosis within the lesion. Tumor resection was unfeasible due to tumor localization with close proximity to the inferior vena cava. Patient underwent transarterial chemoembolization (TACE) treatment twice with substantial tumor necrosis. During 17 years follow up period, patient was asymptomatic and in good physical condition. Long term tumor progression free survival was confirmed by radiological examinations; the HCC disease development occurred 17 years after initial diagnosis.

The presented unique case of large well differentiated HCC identified the low-grade malignancy of HCC as a favorable prognostic factor which was supported by the patient's good performance status and disease progression free survival for 17 years, despite tumor size and only palliative TACE therapy. It is recommended to evaluate these atypical HCC cases in an individual way beside standard prognostic protocols.

**Key Words:** hepatocellular carcinoma, prognosis, transarterial chemoembolization, tumor vascularity, well differentiated

## Introduction

Hepatocellular carcinoma (HCC) represents the fifth most common cancer worldwide and disease classification is mandatory for prognosis assessment and treatment recommendation at any tumor stage. Barcelona Clinic Liver Cancer (BCLC) staging system has been the most accepted model endorsed by the most prominent associations for the study of liver disease, taking in consideration key factors: tumor stage, liver function, patient's performance status and consequently propose the most optimal therapeutic options. BCLC staging system is based on clinical parameters and provides a rational framework for treatment decision (1, 2, 3, 4).

Nevertheless, beside the same disease stage, the different treatment outcome and survival rate in some patients with HCC might be linked to histopathological characteristics as tumor cell grading and tumor vascularity. Number of published articles are giving much attention to the presence of some HCC tumors with favorable clinical course mainly due to the tumor cell differentiation (5, 6, 7).

Well differentiated HCC tends to be slow-growing compared to moderately or poorly differentiated tumors, and conversion to less differentiated may be responsible for cell proliferation and tumor growth. Intratumoral hemodynamic including arterial and portal blood supply to HCC is closely related to malignances grade, where increased arterial vascularity is associated to the decreased tumor cell differentiation (8, 9, 10).

A rare case with a single large tumor measured 9cm in diameter histopathologically defined as well differentiated HCC, with long term of 17 years favorable clinical course is presented.

The aim of this study is to show that pathological features as tumor cell differentiation and tumor vascularity of HCC are factors contributing to prognostic outcome in patient with HCC, beside large tumor size and palliative treatment only.

## Case report

A 52-years-old male was presented with two weeks history of fever, night chills and tenderness in the right upper abdominal quadrant. Laboratory examination revealed elevated white blood cells count ( $17,3 \times 10^9/L$ ), liver function tests within normal limits as well as normal alpha-fetoprotein (AFP) serum level. HBsAg and HBeAg were positive. No clinical or biochemical signs of liver disease were present. Clinical presentation and radiological findings were distinct. Abdominal ultrasound (US) disclosed large tumor measuring 8×9 cm in the right lobe of the liver. Tumor mass presented as a single solid tumor, well defined from the surrounding liver parenchyma with heterogeneous pattern within the tumor. Contrast computed tomography (CT) scan demonstrated large tumor into the posterior segments and showed vague areas of vascularity, predominantly non-enhanced tumor in the arterial phase and without clear associated washout in portal and late venous phase (Figure 1).

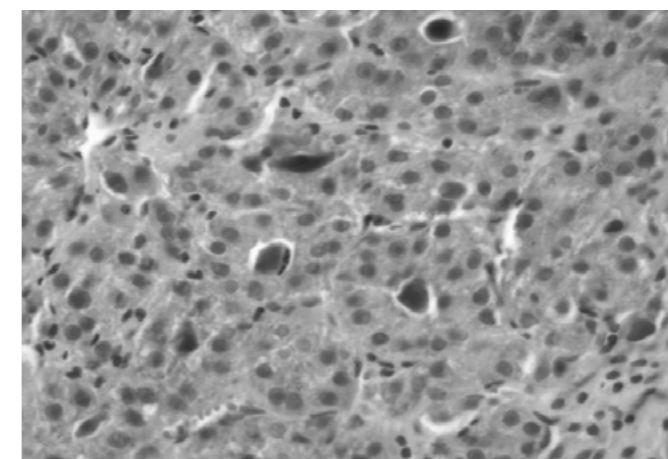
**Figure 1.**



*CT scan demonstrated the presence of a large tumor in the posterior segments, well defined, vague areas of vascularity and necrosis within the lesion. (June 2000 year).*

Radiological findings were not conclusive for diagnosis and fine-needle aspiration biopsy under US guidance was performed. Histopathological examination revealed two fragments of tissue composed of cells that resemble mature hepatocytes with unremarkable cellular atypia, arranged in irregular trabecular and pseudo glandular structures with disturbed histological architecture, findings that defined well differentiated HCC (Figure 2).

**Figure 2.**

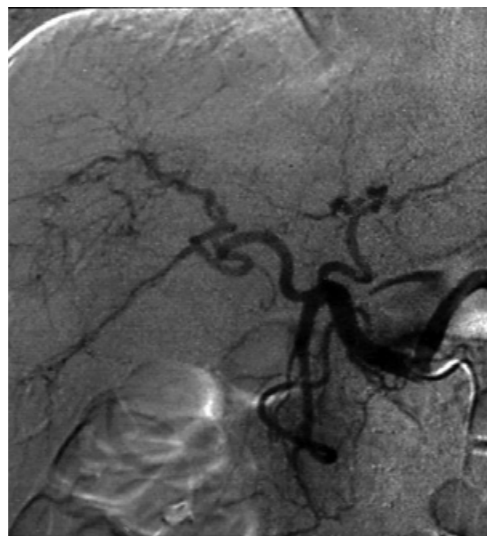


*Biopsy specimen HE stained defined well differentiated HCC characterized by unremarkable cellular atypia, moderate hypercellularity and irregular trabecular and pseudo glandular growth pattern.*

After tumor extension and liver function assessment, surgical treatment was recommended. Patient underwent surgery in a referent center with multidisciplinary team experienced in HCC treatment. Tumor resection was unfeasible due to tumor localization with close proximity to the inferior vena cava. Considering the large size of the tumor TACE treatment was recommended. Patient underwent TACE therapy three days after laparotomy was done. The procedure included

selective catheterization of the hepatic artery branches with local instillation of embolic material Lipiodol 10ml combined with 20mg of chemotherapeutic drug Mitomycin. After chemoembolization, the patient underwent control CT that revealed remarkable treatment response with massive necrosis within the tumor. Five months later, contrast CT detected reduced tumor size with few small vague areas of vascularity and another TACE was performed (Figure 3).

**Figure 3.**



*Transarterial angiography during TACE procedure.*

During the 17 years follow-up period, patient had very good physical performance, without any symptoms, laboratory findings and AFP were within normal range. Abdominal ultrasound exhibited ill-defined mass at the site of previously visible tumor, with no clear margins and heterogeneous pattern within the mass. Contrast CT revealed tumor shrinkage and absence of tumor vascularity, findings that indicated disease/tumor progression free survival (PFS) (Figure 4, Figure 5).

**Figure 4.**



*CT shows tumor with small areas of vascularity within the non-enhanced tumor and areas of Lipiodol accumulation (5 months after primary diagnosis and TACE treatment).*

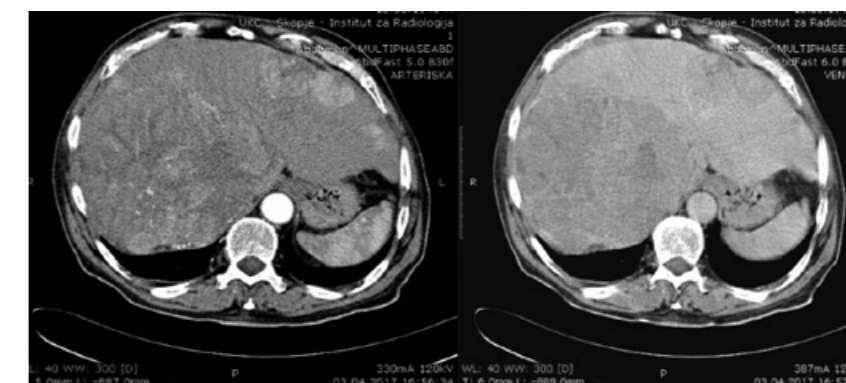
**Figure 5.**



*CT scan shows partial tumor reduction, entirely non-enhanced tumor and areas of Lipiodol accumulation. (10 years after the primary diagnosis).*

Seventeen years later patient was admitted in hospital again, due to fatigue, loss of appetite, weight loss and right leg pain. Laboratory examination revealed anemia, elevated liver enzymes and tumor markers within normal range. Ultrasound disclosed large tumor over 10cm in size localized in the right lobe at the site of previously diagnosed tumor with “nodules in nodules” pattern and few small satellite nodules in the surrounding liver parenchyma. Hypervascular tumor was demonstrated on color Doppler examination. Additionally, a tumor mass measuring 5cm in size was visualized in the pelvic region next to the sacral bone. Contrast CT showed the presence of typical pattern for HCC with contrast enhancement in arterial phase and washout in portal and venous phase and satellite nodules at the vicinity of the main tumor confirming HCC progression (Figure 6). Protruding pelvic tumor attached to the sacral bone was diagnosed as metastasis. Disease stage was categorized as advanced HCC defined by multiple liver tumors, the presence of extrahepatic spread and cancer related symptoms. Systemic treatment with Sorafenib was recommended as standard of care for this stage. Since sacral bone metastasis was cause of a profound pain along the right leg, local radiation treatment was applied. Patient’s condition progressively deteriorated, and five months later he passed away.

**Figure 6.**



*CT scan showed large tumor and few small nodules with typical vascular pattern for HCC with contrast enhancement in arterial phase and washout in venous phase (17 years after the primary diagnosis).*

## Discussion

Once the diagnosis is established, prognostic evaluation is a critical step in the management of HCC. Among the actual staging systems proposed, the most relevant has been the BCLC because of its predictive ability and treatment recommendations (1, 2, 10). Liver function assessment is one of the principal factors for prognosis evaluation, but factors related to HCC tumor burden have a greater prognostic significance in patients with no underlying liver disease or preserved liver function. Evaluation of tumor stage includes tumor size, number of tumors, vascular invasion and extrahepatic spread. Among them, tumor size is a major prognostic factor, with very good prognosis for small HCC (11).

Despite the tumor features integrated in the existing staging systems, histopathological characteristics of the HCC tumors are investigated and discussed as factors correlated to disease prognosis. Recently, clinical practice guidelines in Japan already include a specific algorithm for the diagnosis and treatment of early HCC defined in accordance to the pathological tumor features. Differentiation of the early and very early HCC is based on high grade cell differentiation and the presence of hypovascular tumor (6, 10).

Although small HCC (less than 2 cm) is frequently well differentiated, according to one study among 663 patients with HCC, there were 17 cases with large size well differentiated HCC and the presence of portal perfusion into the tumor. These tumors clinically and histologically display benign nature, and showed extremely slow growth. It is speculated that this large atypical HCC do not undergo the phenotypic change of late-step hepatocarcinogenesis and was recommended to be considered as a new clinical entity (7, 11).

Better prognosis in patients with well differentiated HCC particularly after curative treatments as resection or liver transplantation have been reported. The outcome after hepatic resection was studied retrospectively in 265 HCC patients and showed significantly greater 5-years survival rate in cases with well differentiated HCC (12). A retrospective study of 56 HCC patients who underwent orthotopic liver transplantation is reporting that among multiple factors, tumor cell differentiation had a statistically significant effect on the prognosis (13,14). Tumor cell grading in HCC had a clinical significance and was found to be positively correlated with the invasive proclivity (15, 16, 17).

During multistep hepatocarcinogenesis, the arterial blood flow increases from hypovascular well differentiated HCC to hypervascular classical HCC. During this process the proliferative activity of the tumor cells also increases (9). Contrast CT scan shows characteristic imaging appearance of HCC with hypervascular tumor in arterial phase that shows washout in the portal and late venous phase. Hypovascular HCC on contrast CT is associated with portal perfusion presence (18, 19, 20).

The presented case is peculiar for two reasons: firstly, large tumor size (9cm) pathohistologically defined as well differentiated that does not correlate with common finding for HCC; and secondly, extremely favorable clinical course with almost two decades patient's good performance status and disease progression free survival.

The association of tumor size and cell differentiation has been reported by number of investigators. Small size HCC may differ from well differentiated to less differentiated ones and may present with portal or arterial blood supply. Large size HCC shows mostly moderately or/and poorly differentiated grade, tumor arterial blood supply and neovascularisation (7, 21). Large well differentiated HCC are very rare particularly with size more than 5cm.

TACE therapy is the current standard of care for patients presenting in intermediate stage HCC, as a palliative locoregional therapy that extends survival. Induction of a complete tumor necrosis to enter into a tumor free status is difficult to achieve, especially in large HCC tumors (22, 23, 24). According RTC and meta-analysis of pooled data, TACE extends the survival to a median of up to 20-40 months (25, 26, 27). TACE was optimal therapeutic procedures for the reported case considering the presence of a single large unresectable HCC tumor, preserved liver function, no present extrahepatic spread and good performance status. TACE treatment was performed and induced substantial tumor necrosis evident by absence of contrast enhancement on controlled CT. Interestingly, the presented case showed five times more progression free survival than the data reported in the recent literature. Taking into consideration the large size of the tumor, no presence of marked arterial blood supply and that TACE was performed only twice during the first year of the disease, it appears that procedure alone was not beneficial in terms of improved patient's survival rate, but tumor cell differentiation of HCC was more important.

So far in the literature it has not been described a case as the presented one that underwent only palliative TACE treatment and had 17 years survival rate. The case indicated the significance of tumor's histopathological characteristics. Unfortunately, tumor resection was unfeasible and the detailed examination of the surgical specimen and evaluation of the entire tumor was not available. The disease progression of the presented case was disclosed on contrast CT showing typical pattern for hypervascular HCC.

Biological features and genetic profiling of HCC, last decade were evaluated for early diagnosis, prognostic stratification and treatment strategies with promising results, but are not yet established in the existing staging systems for HCC (28, 29). Some studies suggested the prognostic significance of several molecular markers for the pathological diagnosis of early HCC including; heat-shock protein 70 (HSP70), glypican-3 (GPC3), glutamine synthetase (GS), osteopontin, Golgi protein-73, micro RNAs, VEGF and others (30, 31, 32). Proliferation markers Ki-67 and keratin 19 positively expression is associated with proliferation, differentiation and worse prognosis. Recently, a 5 gene score has been proposed by genetic profiling models, based on the combined expression level of HN1, RAN, RAMP3, KRT19 and TAF9 which are capable of predicting early recurrence and overall survival (33, 34).

The favorable clinical course of the presented HCC case might be better understood by identification of novel biomarkers, molecular and genetic testing not only simply on tumor cell grade, but at the time of primary diagnosis these analyses were not available and there was no tumor samples since resection was not performed. Later on the patient was reluctant for additional

examinations. Therefore further studies including molecular analyses may provide insights into the correlation between pathological parameters of HCC and long-term survival in patients even with large HCC and clarifying the different biological tumor behavior.

In conclusion, the presented unique case of large well differentiated HCC that underwent only palliative TACE treatment identified low grade malignances of HCC as favorable prognostic factor which is supported by the patient's good performance status and tumor progression free survival for 17 years follow-up period. Evaluation of these atypical HCC cases should be done in an individual way beside the standard prognostic protocols.

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## ERECTOR SPINAE PLANE BLOCK AS ADD ON ANESTHETIC TECHNIQUE TO GENERAL ANESTHESIA FOR CHOLECYSTECTOMY

Dimitrovski A<sup>1</sup>, Toleska M<sup>1</sup>, Shoholceva M<sup>2</sup>, Kartalov A<sup>1</sup>, Stefanovski D<sup>1</sup>, Kuzmanovska B<sup>1</sup>  
<sup>1</sup> University Clinic for Anesthesiology, Reanimation and Intensive Care Medicine, University "Ss Cyril and Methodius", Skopje, N. Macedonia  
<sup>2</sup> University Surgery Clinic St. Naum Ohridski, University Ss Cyril and Methodius, Skopje, N. Macedonia

### ABSTRACT

Open cholecystectomy is a surgical procedure which is followed by severe perioperative and postoperative pain. The use of Erector Spine Plane Block (ESPB) as a part of multimodal analgesia in a patient classified as ASA 4, significantly reduced the need for opiates during the operation, as well as in the postoperative period. Erector spinae plane block provides excellent analgesia and cardio circulatory stability during and after the operation. This block can be used as part of multimodal analgesia.

**Key Words:** Analgesia, Erector Spinae Plane Block, Open Cholecystectomy.

### Case Report

The use of ultra sound guided interfascial plane blocks, as part of multimodal anesthesia during abdominal and thoracic surgeries, is new hot topic in anesthesiology, challenging even the "golden standard" - the epidural anesthesia.

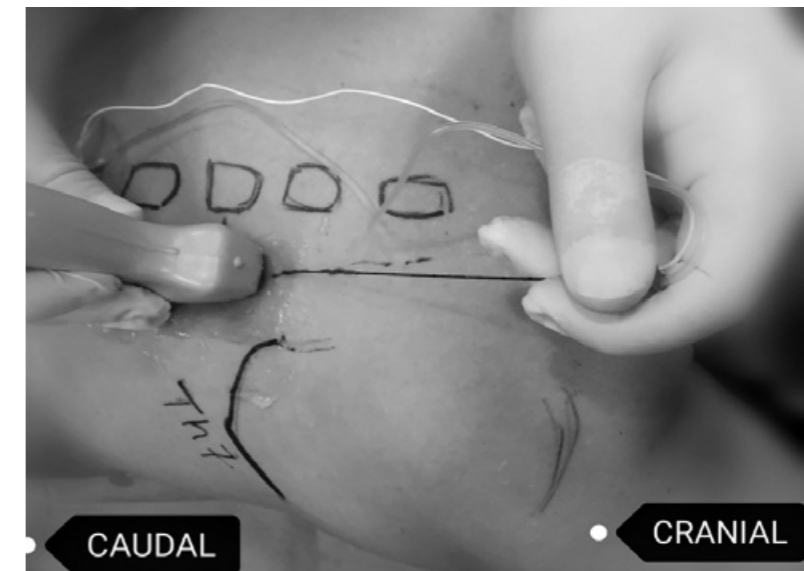
We present a case of 74 years old male patient, ASA physical status grade 4, presented for urgent laparotomy due to acutely inflamed and perforated gallbladder. The patient suffered from CMP, hypertension, pulmonic emphysema and underwent CABG and aortal bi femoral by-pass surgery. The patient was on antiplatelet therapy (Aspirin 100 mg/day), alpha and beta blocker (Carvedilol) and statin therapy.

After obtaining written consent to perform Erector Spinae Plain Block (ESPB), the patient was mildly sedated with Diazepam of 5 mg, monitored for EKG, pulse oximetry and NIBP, and placed in prone position. The patient was breathing oxygen via nasal catheter.

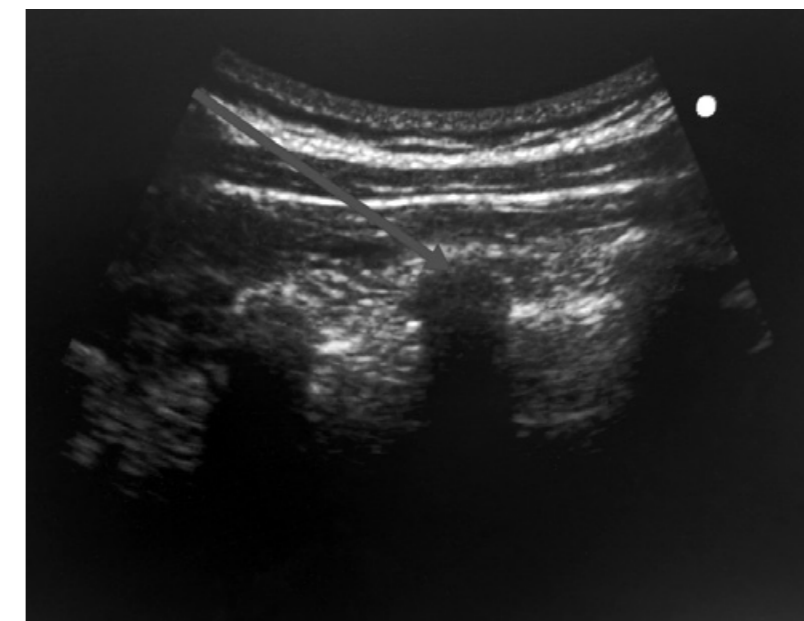
Anatomical landmarks used for ESPB were processus spinosus of the 7<sup>th</sup> thoracic vertebra and the lower edge of the right scapula. The ultrasound probe was placed 3 centimeters lateral

from the 7<sup>th</sup> thoracic vertebra, parallel to the vertebral column, and we identified processus transversus of the vertebra, musculus transversus, musculus rhomboideus and musculus Erector Spinae. Using "in plane" ultrasound technique, we placed the needle 2mm above the processus transversus and applied 20ml Bupivacaine 0.375%, monitoring the distribution of the anesthetic between the fascia of the musculus Erector spinae and the processus transversus.

**Figure 1.** Position of the patient, use of "in plane" technique and anatomical landmarks



**Figure 2.** Ultrasound view of processus transversus of Th7



After the performance of the ESPB, the patient was placed in supine position and introduced in general anesthesia, using low doses of following anesthetic agents: Fentanyl 75micrograms, Ketamine 25milligrams, Lidocain 60milligrams, Propofol 30milligrams, and Succinylcholine



75 milligrams for rapid sequence intubation, followed by rocuronium bromide 40 milligrams and Sevoflurane 1 Vol % and infusion of Remifentanyl 2 milligrams diluted in 40 ml, in rate of 5 ml/h for anesthesia maintenance. Additionally, 1 gram of Magnesium Sulfate was applied, as well as 1 gram of Paracetamol and 100 mg Ketoprofen. Hemodynamics during surgery was stable and BP was monitored via arterial line. The patient was extubated after the surgery and transferred to ward with no pain. The first time patient experienced pain was 7 hours after the surgery, and after receiving 100 milligrams Ketoprofen, the patient was pain free for the following 24 hours. Until the discharge from the hospital, five days after the surgery, the total amount of analgesics that the patient received was 400 mg Ketoprofen and 100 milligrams Tramadol.

### Discussion

ESPB is a new interfascial block, introduced by Forero and his associates in 2016 for treatment of neuropathic pain (1). Since then, ESPB was used by many anesthesiologists as anesthetic technique for different kind of surgeries, expanding its use and its possibilities both in surgery and in pain management (2). So far, two studies were conducted using bilateral ESPB as supplement to general anesthesia for cholecystectomy, one in adults and the other in children (3,4). We used unilateral ESPB for urgent laparotomic cholecystectomy in patient with severe comorbidities and on antiplatelet therapy. The surgery went uneventful, with very low doses of opiates and inhalational anesthetic, and the patient was pain free for 7 hours after surgery. He received very little analgesics during his hospital stay and was discharged on the fifth postoperative day.

### Conclusion

ESPB is safe regional anesthetic technique to use as supplement to general anesthesia for patients on antiplatelet therapy. Larger studies are needed to establish the value of ESPB as add – on anesthetic technique to general anesthesia for laparotomy.

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## THE VALIDITY OF MAGNETIC RESONANCE IMAGING IN DETERMINING PREOPERATIVE T STAGE OF RECTAL CANCER

Lazarova A<sup>1</sup>, Saliu V<sup>2</sup>

<sup>1</sup> University Clinic of Surgery St. Naum Ohridski, Skopje, Department for Radiology.

<sup>2</sup> University Clinic of Surgery St. Naum Ohridski, Skopje, Department for Abdominal Surgery

### ABSTRACT

**Introduction:** The significance of preoperative staging of rectal cancer with magnetic resonance imaging is initial for the decision on further treatment of the disease, simple surgical or multimodal treatment at an advanced stage of rectal cancer.

**Aim of the Study:** This paper demonstrates the validity of magnetic resonance imaging in determining the T stage of rectal cancer preoperatively, in correlation to the findings from the operative pathohistological material.

**Material and Methods:** 82 patients aged from 43 to 87 years, with previously colonoscopy proven rectal cancer were treated in magnetic resonance imaging (MRI) – 1.5 T, standard pulls sequences were made: SAG T2, AX T1, AX T2, AX DWI and T stages were determined.

**Results:** The results obtained for the T stage with magnetic resonance are correlated to the pathohistological finding taken postoperatively as the gold standard in determining the sensitivity and specificity of magnetic resonance imaging. The sensitivity of MRI in determining the rectal cancer at T1 and T2 stage carcinomas was 86.7% and the specificity was 98.5%. The sensitivity of MR in determining T3 stage rectal cancers was 89.1% and the specificity was 88.9%. The sensitivity of MR in determining the T4 stage rectal cancers was 91.7% and the specificity was 92.9%.

**Conclusion:** Magnetic resonance imaging is the gold standard in preoperative staging of rectal cancer.

**Key Words:** magnetic resonance image, preoperative staging, rectal cancer.

## Introduction

Rectal cancer is an advanced malignancy with a high mortality rate in developed countries. There is a slightly higher predisposition to the male sex (on average 20% – 30% is higher in men than in women), and the percentage of the disease is higher than 50 years of age – the average age of the disease worldwide is 65 years (1).

However, although the incidence of the disease has increased, the mortality rate has decreased due to several significant factors (2). Firstly adenosis polyps that are considered precancerous lesions are detected by colonoscopy and can be removed (3). Also, preoperative staging of rectal cancer with magnetic resonance imaging (MRI) plays a significant role in the further multimodal and surgical treatment, which affects the reduction of extensive surgical treatment, increasing the 5-years survival rate, reducing the recurrence rate (4).

Rectal cancer prognosis has improved significantly over the past decade, largely thanks to advances in preoperative staging, which has reflected a therapeutic approach that has made significant changes from simple surgical treatment to multimodal treatment (5). The result is an increase in the five-year survival rate and a reduction in the recidivism rate, the percentage of multivisceral and more extensive resections in the surgical treatment of rectal cancer also decrease (6, 7).

The goal of neoadjuvant therapy is to reduce the size and stage of advanced rectal cancer, minimize the risk of distant metastases, and to provide less extensive surgical therapy and, preferably, sphincter reservation technique for tumors localized in low rectum. The question is whether a patient with rectal cancer is a candidate for surgery treatment alone or preoperative chemoradiotherapy followed by surgery (8).

MRI can answer this question because it is the most important tool in the staging of rectal cancer. Magnetic Resonance Imaging method plays a crucial role in preoperative staging of rectal cancer (3, 4).

MRI is the modality of choice for rectal cancer staging, which assists the surgeon in achieving the negative margins of resection (9, 10).

## Material and Methods

This paper shows the results of 82 patients diagnosed with rectal cancer by colonoscopy. Magnetic resonance imaging was performed preoperatively to determine the stage of the disease that would further influence the decision on treatment of the disease, whether it would be only surgical, or preoperative neoadjuvant treatment then followed by surgery.

This paper demonstrates the sensitivity and specificity or validity, accuracy of magnetic resonance imaging in determining the preoperative T stage of rectal cancer. A comparison was made between the results for the T-stage performed by magnetic resonance imaging preoperatively to the results obtained from the pathohistological operative finding, which was taken as the gold standard on the basis of which the correlation was made.

The examination was made on a 1.5 T magnet in the University Clinic for Surgical Diseases St. Naum Ohridski, Skopje.

Inclusive criteria for participation in these series were: patients with colonoscopy proven rectal cancer in whom pre-operative staging with MRI was indicated.

Patients excluded from this study were those who, due to implanted metal parts were contraindicated in performing the examination and those who could not withstand the examination due to claustrophobia.

The standard MRI protocol included:

SAG T2 pulse sequence, which starts the examination and determines the localization of the tumor in the rectum. A tumor localized in the low rectum is up to 5 cm from the anorectal junction, a tumor localized in the middle rectum is 5 to 10 cm, and above 10 cm is a high rectum.

Based on the SAG T2 pulse sequence, AX T1, AX T2 and AX DWI were performed. In these pulse sequences, the T stage is determined first (11, 12).

It is not possible to determine the exact T1 and T2 stage of MRI, so it is not possible to say with certainty whether the tumor grows in the submucosa or invades the external muscularis.

T3 stage is when the tumor penetrates the rectal wall and grows into the mesorectal adipose tissue. This is a heterogeneous group in terms of division depending on the localization to the mesorectal fascia, which is the most important in preoperative staging to determine preoperative neoadjuvant treatment. If the tumor is less than 2 mm from the mesorectal fascia nearby, or infiltrates it, it is a potential seizure that requires preoperative neoadjuvant treatment. T4 stage is when the tumor grows in neighboring organs (vagina, uterus in women, prostate in men as well as in muscular and pelvic organs) (13, 14).

### Statistics Analysis:

The obtained data are analyzed with statistical computer program SPSS 23.0 for Windows. Numerical marks are shown with arithmetic mean and standard deviation; Independent parameter and non-parameter tests (Chi-square test, Fisher exact test, test, Student t-test, Analysis of Variance) are used to compare the analyzed variables. Spearman's correlation coefficient is used to determine the correlation between certain variables. To determine the diagnostic performance of MRI in determining T status of rectal cancers, sensitivity, specificity, positive, and negative probability rates are calculated. The  $p < 0.05$  values are taken to be statistically significant.

## Results

The study included 82 patients from the University Clinic for Surgical Diseases St. Naum Ohridski in Skopje, as well as patients from the Clinic for Abdominal Surgery at the University Clinic – Skopje, with colonoscopically confirmed rectal cancer.

The gender structure of the patients consisted of 58.5% (48) male patients, and 41.5% (34) patients were female. Patients ranged in age from 43 to 87 years, and averaged  $66.65 \pm 9.8$  years.

According to the preoperative MRI finding, T3 stage was the most common finding in the respondents – 63.4% (52) patients, 19.5% (16) patients had T4 stage rectal cancer, 13.4% (11) patients had second stage rectal cancer, and in 3.7% (3) patients MRI detected malignant rectal disease in the first stage

**Table 1.** Distribution of the respondents by T staging – MRI

MRI/T stage	n (%)
T1	3 (3.66)
T2	11 (13.41)
T3	49 (59.76)
T4	16 (19.51)
T3b	3 (3.66)

The pathohistology results presented 67.1% (55) rectal cancers in T3 stage, 14.6% (12) in T4 stage, much fewer patients had rectal cancer in the first and the second stage – 8.5% (7) and 9.8% (8) consequently.

**Table 2.** Distribution of the respondents by T staging-pathohistology

Pathohistology stage	n (%)
T1	7(8.54)
T2	8 (9.76)
T3	55 (67.07)
T4	12 (14.63)

The Table 3 shows the cross-tabulated distribution of the T stage determined preoperatively with MRI and pathohistology. The results show that all 3 tumors were preoperatively diagnosed with MRI as T1 stage and were pathohistology confirmed. In the group of 11 tumors preoperatively with MR marked as T2 stage, 6 were also pathohistology confirmed. In the group of 52 tumors preoperative with MR detected as T3 stage, 49 were also pathohistology confirmed. In the group of 14 tumors, preoperative with MR detected as T4 stage, 11 were pathology confirmed.

**Table 3.** Distribution and correlation by T stage – MRI / pathohistology

MRI T stage	Pathohistology T stage				Total
	T1	T2	T3	T4	
T1	3 (42.86)	0	0	0	3
T2	4 (57.14)	6 (75)	1 (1.82)	0	11
T3	0	2 (25)	49 (89.09)	1 (8.33)	52
T4	0	0	5 (9.09)	11 (91.67)	16
variable	correlation				
	N	Spearman – R	p-level		
T stage MRI& Pathohistology T stage	82	0.854	p=0.000000 sig		

A positive or direct correlation was confirmed between the preoperative MRI T stage and the pathohistology T stage (R=0.854). For a value of  $p < 0.001$ , the correlation was statistically significant.

With MRI, 14 findings were detected as the first and the second stage, of which 13 were true positive, confirmed and pathohistologically, one result was false positive. The MRI finding presented 68 tumors that were not of the first and the second stage, of which 66 were true negative, confirmed also with pathohistology, 2 findings were false negative.

The sensitivity of MRI in determining rectal cancer at T1 and T2 stage carcinomas was 86.7% and the specificity was 98.5%

**Table 4.** MRI Validity for determination T1 and T2 stages of rectal cancer

MRI T staging	Pathohistology T staging		Total
	first and second stage	the rest	
first and second stage	13	1	14
the rest	2	66	68
Total	15	67	82
Estimate	95% CI		
Sensitivity	0.867	[0.621 to 0.963]	
Specificity	0.985	[0.92 to 0.97]	
LR+	57.8	[8.217 to 410.335]	
LR-	0.135	[0.037 to 0.492]	

The Table shows the results of the examined MR validity in detecting the third stage rectal cancers.

With MRI, 52 findings were detected as the third stage, of which 49 were true positive, confirmed and pathohistologically, 3 were false positive. With MR 30 results were not marked as the third stage, of which 24 were truly negative, so confirmed and pathohistology as another stage, 6 findings were falsely negative.

The sensitivity of MR in determining T3 stage rectal cancers was 89.1% and the specificity was 88.9%.

**Table 5.** MRI Validity for determination T3 stages of rectal cancer

MRI T staging	Pathohistology T3 stage		
	third stage n (%)	the rest n (%)	total
third stage	49	3	52
the rest	6	24	30
total	55	27	82
Estimate	95% CI		
Sensitivity	0.891	[0.782 to 0.949]	
Specificity	0.889	[0.719 to 0.961]	
LR+	8.027	[2.748 to 23.396]	
LR-	0.123	[0.057 to 0.264]	

The Table shows the results of the examined validity of MRI in detection of rectal cancer in the fourth stage. With MRI, 16 findings were detected as the fourth stage, of which 11 were true positive, confirmed and pathohistology, 5 findings were falsely positive. With MRI, 66 of the results were not marked as the fourth stage, of which 65 were truly negative, confirmed and pathohistology as another stage, 1 result was falsely negative. The sensitivity of MRI in determining T4 stage rectal cancers was 91.7% and the specificity was 92.9%.

**Table 6.** MRI Validity for determination T4 stages of rectal cancer

MRI T4	Patohistology T4 stadium		total
	T4	others	
T4	11	5	16
others	1	65	66
total	12	70	82
Estimate	95% CI		
Sensitivity	0.917	[0.646 to 0.985]	
Specificity	0.929	[0.843 to 0.969]	
LR+	12.915	[5.421 to 30.379]	
LR-	0.089	[0.014 to 0.587]	

## Discussion

This study shows that MRI is an ideal tool in preoperative staging of rectal cancer. It is the gold standard in preoperative evaluation of the stage of the disease. The anatomical localization of the rectum, its fixation on the pelvic floor and fat tissue, as well as the absence of peristalsis, which avoids moving artifacts, makes it an ideal organ for recording with the MRI imaging method. This method is extremely important in the diagnosis and staging of rectal tumors (15, 16).

What is the most significant in preoperative staging of rectal cancer with MRI is its accuracy or sharpness, validity in relation to the T stage, which was actually one of the main motives for making this study.

The postoperatively obtained pathohistology finding was taken as the gold standard in relation to which correlation was made with the findings from MRI with respect to T stage. In this study of 82 treated patients, out of which 14 patients are in T1 and T2 stage, 13 of them are positive and confirmed pathohistology, one is false positive. The sensitivity of MRI in determining the first-and the second-stage rectal cancer is 86.7% and its specificity is 98.5%.

This result correlates to paper from Torricelli P (2007), where the endorectal coil MRI in local staging of rectal cancer, was mentioned with the sensitivity of 86% and specificity is 97%.

With MRI, 52 findings were detected as the third stage, out of which 49 were true positive, confirmed and pathohistology, 3 were false positive. With MRI 30 results were not marked as the third stage, out of which 24 were truly negative, confirmed and pathohistology as another stage, 6 findings were falsely negative.

The sensitivity of MRI in determining the third-stage rectal carcinomas was 89.1% and the specificity was 88.9%.

According to the results from the paper of Klessen C at all (2007), the sensitivity ranges between 85%-89% and the specificity around 94% for T3 stage.

With MRI, 16 findings were detected as the fourth stage, out of which 11 were true positive, confirmed and pathohistology, 5 findings were falsely positive. With MRI, 66 of the results were not marked as the fourth stage, out of which 65 were truly negative, confirmed and pathohistology as another stage, 1 result was falsely negative. The sensitivity of MRI in determining the fourth-stage rectal carcinomas was 91.7% and the specificity was 92.9%.

Therefore, the results obtained in this study on the sensitivity and specificity of preoperative T-staging with magnetic resonance imaging show great validity, significance, and accuracy of preoperative T-staging of rectal cancer with magnetic resonance imaging, thereby confirmed this method as great diagnostic tool for preoperative staging of rectal cancer.

## Conclusion

MRI is a high-precision imaging method for detection of transmural tumor invasion, invasion of the mesorectal fascia, involvement of adjacent organs, insight into nodal status, and visualization of a positive extra mural vascular invasion. MR as an ideal imaging method for preoperative staging for local or advanced stage of rectal cancer, allows the evaluation of extramural expansion, determines the mesorectal involvement and seizures margins of resection.

This is evidenced by the high sensitivity (83% – 89%) and specificity (up to 96%) for T-staging. Knowledge of these factors is essential in the treatment of rectal cancer. The aim of staging of rectal tumors with MRI imaging method is to identify patients in the T3 stage with potentially involvement in resection margins and T4 stages in order to benefit from radiation and radiotherapy.

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## IPOM PLUS – AN EFFECTIVE METHOD IN TREATMENT OF VENTRAL HERNIA

Mitevski A<sup>1</sup>, Antovic S<sup>2</sup>, Markov P<sup>3</sup>

<sup>1</sup> General Hospital RE-MEDIKA, Skopje, Macedonia. Assistant professor at “Goce Delcev” University, Shtip, Macedonia.

<sup>2</sup> Clinic for Digestive Surgery, Medical Faculty Skopje.

<sup>3</sup> General Hospital Strumica, digestive surgery resident, “GoceDelcev” University, Shtip, Macedonia.

### ABSTRACT

**Introduction:** Abdominal wall surgery for ventral hernia is one of the commonest procedures performed by surgeons. Hernias that occur after previous abdominal surgery - incisional hernias - appear in 11% to 20% of the cases, and the recurrence of ventral hernia is related to the presence of abdominal rectus muscle diastasis.

**Case:** A patient who had two previous operations for ventral hernia with prosthesis was admitted. Hernia bulging and partially reducing content of the hernia sac when pressure applied was present. Intraoperative, a recurrent hernia was observed and pseudohernia – bulging out of the previous implanted prosthesis was noted, cephalic from the clinically diagnosed defect. Also a rectus muscle diastasis was present caudally.

**Discussion:** The laparoscopic IPOM repair is associated to a high incidence of post-operative bulging or eventration of mesh, seromas, recurrences and non-restoration of abdominal muscle function. To overcome these problems, sutured closure of the defect in the fascia with intra-peritoneal mesh reinforcement has been described, known as the IPOM plus repair. This repair is the recommended procedure in the guideline of International Endohernia Society.

**Conclusion:** In patients who are presented with diastasis of the abdominal rectus muscles in addition to the ventral hernia, plication of the diastasis can be done in order to help support of the ventral hernia and improve outcomes or can be sutured with transfascial non-absorbable single sutures along the diastasis. It brings considerable esthetic advantages and reduces the recurrence of hernias.

**Key Words:** IPOM plus, laparoscopic ventral hernia repair, mesh repair, rectalis muscle diastasis, ventral hernia,

## Introduction

Abdominal wall surgery for ventral hernia is one of the commonest procedures performed by the surgeons. The surgical procedures that are the most often encountered in adults are repair of incisional hernias and surgery for paraumbilical hernia. Hernias that occur after previous abdominal surgery - incisional hernias appear in range from 11% to 20% of the cases (1, 2, 3). Minimal invasive surgery, e.g. laparoscopy performed in such hernias has an advantage in shorter hospital stay, lower wound infection, earlier recovery and in recurrence rates of less than 5% compared to the open repair (4, 5, 6). We have to stress here that the recurrence of ventral hernia is related to the presence of abdominal rectus muscle diastasis.

## Case

We present a case of a fifty-years-old patient, admitted for elective treatment of second recurrence of an incisional hernia. The patient had two previous operations in which a prosthetics were used, placing the mesh underlay. Clinically hernia bulging caudally from the umbilicus was seen and on applied pressure partial reduction of hernia sac content was present. Also a rectus muscle diastasis was present cranially. CT (computed tomography) was performed and a hernia defect supraumbilical was confirmed with proximal diastasis of the abdominal rectus muscles, cranial defect with eventration of the mesh was not noted, just some irregularity of the fascia that we considered as fibrosis (Figure 1). After appropriate pre-operative preparation, the patient was operated under general anesthesia.

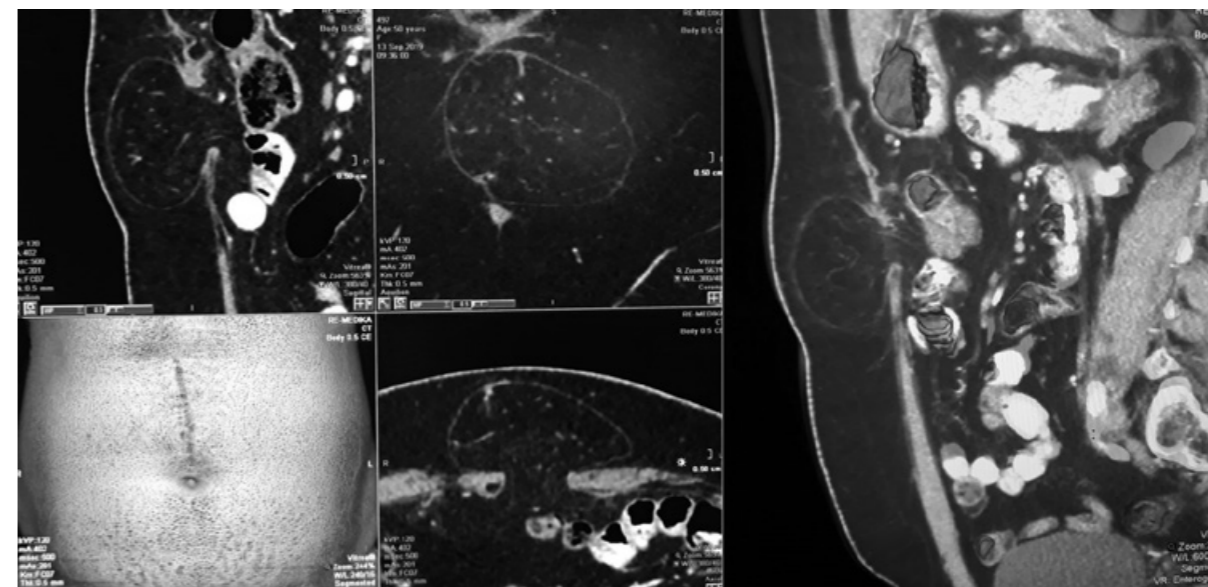
A 10-12 mm incision was made on the Palmer's point, 3cm below left sub costal margin on the midclavicular line. A Veress needle was inserted and pneumoperitoneum of 12 mm/Hg was achieved. A 10 mm trocar was inserted through the same incision site. Inspection of the abdominal cavity revealed adhesions of the omentum to the anterior abdominal wall at the site of the previous surgery. Under visualization, two more 5mm trocars and one 10mm trocar were placed on the left anterior axillary line.

A sharp dissection of the adhesions on the anterior abdominal wall was performed. Umbilical recurrent hernia was present with previous mesh pushed or migrated laterally to the right and cranially. Also a pseudohernia or eventration of the mesh was noted, bulging out of the previous implanted prosthesis (the second implanted mesh) cephalic from the clinically diagnosed defect (Figure 2).

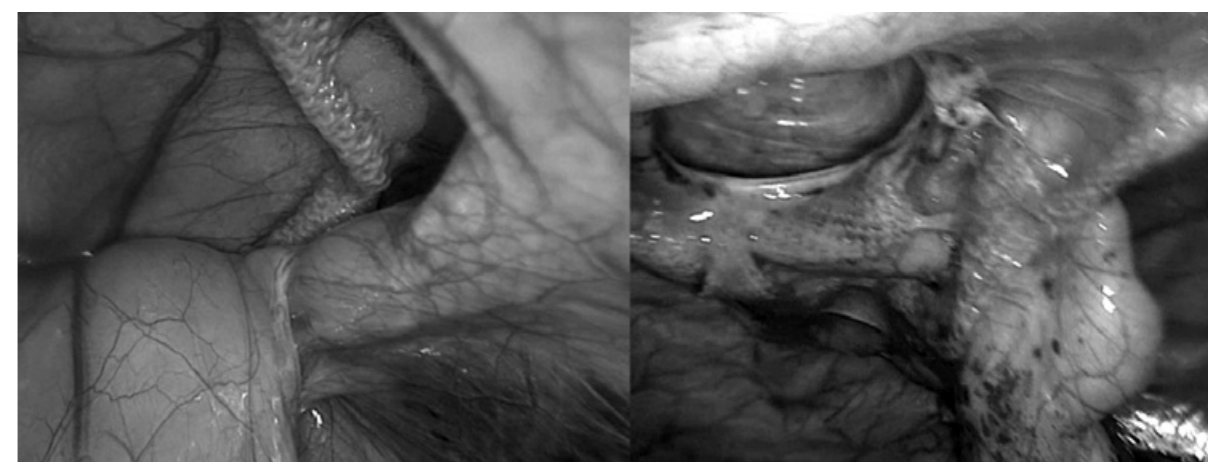
Additional weakness of the linea alba was noted, the most clearly presented cranially from the site of the previous surgery.

Using endoclose needle, single sutures were applied to plicate the linea alba, as well as for approximation of the edges of the hernia rings. Once the mesh was inserted into the abdomen, four transfascial sutures were used to anchor the mesh to the anterior abdominal wall, followed by additional fixation with tackers. (Figure 3). Partial covering of the mesh with previously dissected peritoneum from falciform and umbilical ligament was performed.

*Figure 1. CT, supraumbilical hernia and irregularity cranially (right)*



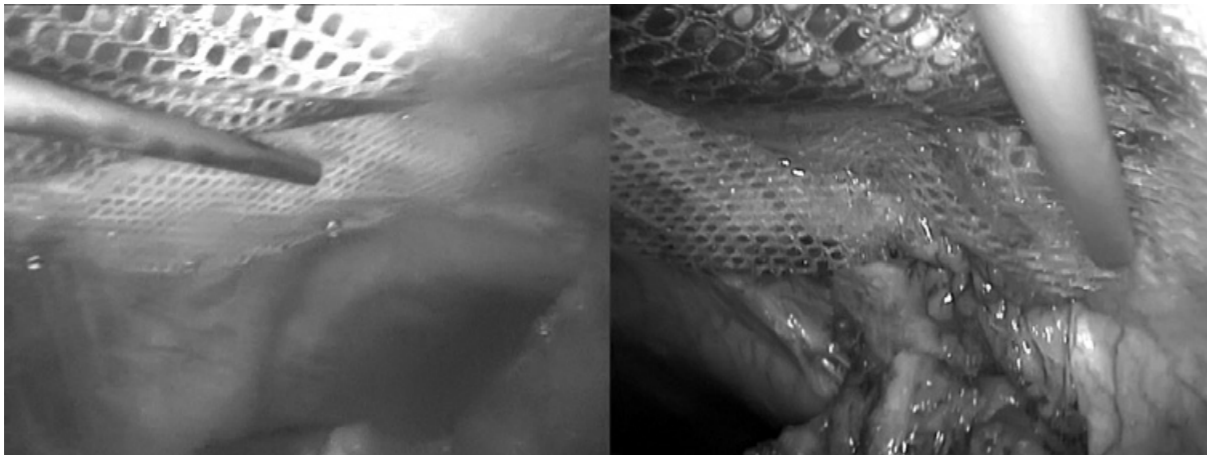
*Figure 2. Cephalic midline defect with visible bulging of the prosthetic material (left) and caudal midline defect with hernia ring and visible prosthetic material (right)*



## Discussion

From the beginning laparoscopic repair of ventral hernias was only bridging the defect from the peritoneal side with a mesh that had ability to prevent visceral adherence to it. The procedure was named IPOM repair (Intra-Peritoneal On-lay Mesh repair). It was performed with intra-peritoneal, laparoscopic approach, and the placement of the mesh was in underlay fashion on the parietal peritoneum. According to the literature this kind of repair has a high incidence of bulging or eventration of the mesh, fluid collection in the residual hernia sac (seroma), recurrence and non-restoration of abdominal muscle function (7, 8, 9). To overcome all of these problems, IPOM plus technique was introduced. It is consisted of closure of the hernia defect with additional intra-peritoneal mesh reinforcement (10). This repair is recommended in the guidelines of International Endohernia Society (11).

**Figure 3.** Mesh fixation on anterior abdominal wall using titanium tackers



Complex abdominal wall hernias present a serious problem in the means of surgical treatment, both conventionally and laparoscopy addressed. The defect on the abdominal wall-hernia ring, especially when treated with IPOM technique as only a bridging method, has influence on the shear forces to the mesh and the anchoring points, therefore a bulging phenomenon is much likely to occur in larger defects (12). Also, the mesh overlaps of the borders of hernia ring is important as a factor, and depends on the size of the hernia defect. The larger the gap - hernia ring, more overlapping of the mesh is needed (13,14). When we think of standard IPOM technique, we know that it has a limit when dealing with large defects. Therefore a technique where hernia gap is closed, linea alba is reconstructed, a sufficient overlap of the mesh is possible, and also a morphological and functional reconstruction of the abdominal wall is achieved. This technique performed in minimally invasive manner multiplies the advantages like lower wound infection rate, occurrence of seroma and thereafter - shorter hospital stay. The technique first described by Chelala, today is known as IPOM plus technique. When compared to the retro muscular hernia repair like Rives–Stoppa technique, this method does not disturb muscle compartments or the segmental nerve innervations (12, 15, 16). This is in particular important in cases where previous operative interventions were performed, thus making the sub lay compartments not easy to access. When dealing with very large hernia defects this technique reaches its limits. With this particular patient we used a surgical technique in which we do a laparoscopic closure of the linea alba with transfascial, non-resorbable single sutures, and final reinforcement by an intraperitoneal - onlay mesh. Prior to mesh application, a detailed anterior wall inspection is conducted.

### Conclusion

In conclusion, in patients who present with diastasis of the abdominal rectus muscles in addition to the ventral hernia, plication of the diastasis can be done in order to help support of the ventral hernia and improve outcomes or it can be sutured with transfascial non-absorbable single sutures along the diastasis. This kind of approach to midline hernias associated with diastasis of the

abdominal rectus muscles is a feasible and reproducible method. It brings considerable esthetic advantages and reducing the recurrence of hernias.

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## INTRA-ARTICULAR BUPIVACAINE PLUS MORPHINE VERSUS BUPIVACAINE ALONE FOR LOCAL ANESTHESIA IN KNEE ARTHROSCOPY

Andonovski A<sup>1</sup>, Popovska D<sup>1</sup>, Andonovska B<sup>1</sup>, Milankov M<sup>2</sup>

<sup>1</sup> University Clinic for Orthopedic Surgery, Traumatology, Anesthesiology and Intensive Care, Skopje, Republic of North Macedonia

<sup>2</sup> University Clinic for Orthopedic Surgery and Traumatology, Novi Sad, Serbia

### ABSTRACT

**Background:** For knee arthroscopy under local anesthesia, the lowest anesthetic concentration with a less chondrotoxic and good analgesic potency should be chosen.

**Purpose:** The aim of the study was to compare the results in patients where knee arthroscopy under local anesthesia was conducted using intra-articular injection of bupivacaine plus morphine versus bupivacaine alone.

**Methods:** The study included 24 patients with a mean age of 27 years undergoing knee arthroscopy under local anesthesia because of meniscus, cartilage and anterior cruciate ligament injury or synovial plica syndrome. Patients were divided into two groups: Group B where local anesthesia was performed using 20ml of 0.5% bupivacaine with adrenaline for intra-articular application, and Group BM where local anesthesia with intra-articular application of 10ml of 0.5% bupivacaine with adrenaline plus 4mg morphine was used. Intra-operative and post-operative pain as well as pain during treatment of different knee pathologies were evaluated using visual analog scale (VAS). Side effects, patients' satisfaction and time for rescue analgesia were also recorded.

**Results:** Patients from group BM had significantly lower mean VAS values than those from group B after 5 (p=0.000) and after 9 (p=0.02) hours from the surgery. The time for rescue analgesia was significantly longer in patients from group BM compared to those from group B (p=0.012). There was no significant difference between groups according to the patients' subjective satisfaction and side effects occurrence. **CONCLUSION:** Solution of bupivacaine plus morphine was more effective than solution of higher concentration of bupivacaine obtaining better postoperative analgesia reducing the risk for chondrotoxicity.

**Key words:** bupivacaine versus bupivacaine plus morphine solutions, clinical results, knee arthroscopy under local anesthesia

### Introduction

Knee arthroscopy is a minimally invasive orthopedic procedure with diagnostic and therapeutic role. It can be performed under general, regional (spinal or epidural) or local anesthesia. The most of the orthopedic surgeons prefer general or regional anesthesia mostly due to the fear of insufficient anesthesia, patient discomfort and unsuccessfully performed arthroscopy with an increased number of rearthroscopies. Analyzing 6519 patients, Forssblad *et al.* concluded that only 0.9% of the primary arthroscopies under local anaesthesia could not be performed safely due to patient discomfort (1). Also, there was no difference in the frequency of rearthroscopy between the arthroscopies performed under local anaesthesia and those performed under general anaesthesia (0.46% vs 0.45%). Studies by Maldini and Kan-Yip Law showed that more than 93% of patients where knee arthroscopy was performed under local anaesthesia were either satisfied or very satisfied with their anesthesia and agreed to have the same procedure performed under local anesthesia in the future (2, 3). According to Jacobson, elective knee arthroscopy can be performed successfully under local anesthesia in 92% of patients from a technical point of view, but patients with gross knee deformity (severe varus or valgus) as well as those with extensive hypertrophic synovitis of the knee are not a good candidates for knee arthroscopy under local anesthesia. Maldini *et al.* showed that local anesthesia provided better and longer analgesia than regional and general anesthesia after knee arthroscopy reducing the use and possible side effects of oral and intravenous analgesics such as nausea, vomiting, drowsiness, and urine retention (4,5).

For successful knee arthroscopy under local anesthesia in addition to the proper patient selection and technical details knowledge, the right anesthetic choice is very important. Although different anesthetics (lidocaine, bupivacaine, ropivacaine, mepivacaine) with different concentration have been proposed, all of them are administrated in the same manner (intra-articular and on the portal site), always mixed with epinephrine. It is considered that by slowing anesthetic release into the vascular system by vasoconstriction, epinephrine improves the efficacy of the local anesthetic and protects from systemic toxicity (6, 7). Weiker used mixed solution of 25ml of 1% lidocaine and 25ml of 0.25% bupivacaine with epinephrine; Iosifidis used mixed solution of 10ml of 2% lidocaine and 10ml of 0.5% bupivacaine with epinephrine; Misculin, Maldini and Shaukat used mixed solution of 20ml of 2% lidocaine with epinephrine and Law used 30ml of 1% lidocaine with epinephrine (2, 8, 9, 10, 11). All these authors presented satisfactory results in the operated patients with a success rate over 94%. Some authors showed that 0.5% concentration of bupivacaine gives better analgesic effect than 0.25%, because higher concentration transverses the synovium more rapidly to reach the joint capsule, which is perforated by articular vessels and nerve endings (12, 13). Although lidocaine and bupivacaine are the most used anesthetics for knee arthroscopy under local anesthesia due to their low cardiac toxicity, high and long-lasting local concentration with prolonged analgesic effects and a low systemic level, the results obtained in the latest studies have shown that lidocaine and bupivacaine are more chondrotoxic than ropivacaine and mepivacaine. It is a general conclusion that lidocaine, bupivacaine,



ropivacaine and mepivacaine are chondrotoxic in a time-dependent, concentration-dependent, and drug-dependent manner and that cellular death rates are higher in osteoarthritic compared to intact cartilage after local anesthetic treatment (11, 14-21). Since chondrotoxic and analgesic potencies do not directly correlate, the lowest anesthetic concentration with a less chondrotoxic and good analgesic potency should be chosen (14).

In order to increase the effects, prolong the analgesic time of local anesthetics and to decrease the necessary concentration of the local anesthetic decreasing the risk of chondrotoxic influence, many drugs have been administered intra-articularly in combination with the local anesthetics. These drugs included opioids (morphine, fentanyl), magnesium sulfate, steroids, and  $\alpha_2$  agonists (clonidine, dexmedetomidine) (22). Opioids can produce potent analgesic effects by interacting with local opioid receptors in inflamed peripheral tissue. The analgesic activity occurs without activation of opioid receptors in the central nervous system (CNS), and therefore centrally mediated side effects, such as respiratory depression, mental clouding, altered consciousness, or addiction, are not associated to the peripheral opioid activity (23, 24). Stain *et al.* showed that morphine injected intra-articularly can provide delayed onset of analgesic peak action at 3–6 h, and pain relief up to 24 h or even 48 h, without causing chondrotoxicity (17, 25, 26).

The aim of our study was to compare the results after intra-articular injection of bupivacaine plus morphine versus bupivacaine alone for local anesthesia in patients undergoing knee arthroscopy.

## Methods

The study included 24 patients (18 men and 6 women) with a mean age of 27 years (range 18 to 32 years) undergoing arthroscopic knee surgery under local anesthesia because of meniscus, cartilage and anterior cruciate ligament injury or synovial plica syndrome (SPS). Exclusion criteria were: allergy to the used drugs, infection at the portal sites of injection, any previous surgery to the knee, patients with chronic extensive synovitis or gross deformity of the knee (severe varus or valgus knee), psychological problems, severe systemic disease, long-term treatment with analgesics, consumption of analgesics or non-steroidal anti-inflammatory drugs within 24 h of surgery, bleeding diathesis or coagulopathy. Preoperative assessment included medical history, clinical examination, detailed laboratory investigations, radiography (RTG) and magnetic resonance imaging (MRI) of the knee and electrocardiogram (ECG). Prior to surgery by a closed envelope technique, patients were divided into two groups: Group B where local anesthesia was performed using 20ml of 0.5% bupivacaine with adrenaline for intra-articular application, and Group BM where local anesthesia with intra-articular application of 10ml of 0.5% bupivacaine with adrenaline plus 4mg morphine was used. In all patients, arthroscopic knee surgery under local anesthesia was performed in the period from February 2019 to February 2020 at the University Clinics for Orthopedic Surgery in Skopje and Novi Sad. All patients preoperatively voluntarily signed a document for informed consent.

## Anesthetic application technique

After cleaning the skin with a sterilizing solution, the skin and the subcutaneous tissues at antero-medial and antero-lateral portal sites were anesthetized with 10ml solution of 2% lidocaine with adrenaline 1:200,000 (5ml at each portal site). Intra-articular application of the anesthetic included 20ml solution of 0.5% bupivacaine with adrenaline (1:200,000) in patients from group B and 10ml of 0.5% bupivacaine with adrenaline (1:200,000) plus 4mg morphine in patients from group BM. We were careful to inject the prepared solution into the joint intra-articular and not into the subcutaneous tissue, especially for muscular patients. About 15 to 20 minutes were necessary for anesthesia to take effect. Intravenous sedation with propofol was used in apprehensive patients to manage their low-grade irritability. In patients with severe irritability that impeded the surgical maneuver and meant technique failure, switching to general anesthesia was proposed. Tourniquet was not used. Adrenalin mixed into the irrigation fluid was used in patients with pronounced bleeding during the arthroscopic surgery.

## Evaluation

Intra-operatively we asked patients to describe the pain at each step of the procedure. We noted the pain according to the visual analog scale (VAS) where 0 represents no pain and 10 represents the worst pain imaginable (27). When there were several pathologic lesions in the knee joint, we identified the primary lesion by probing with an instrument and then evaluated the quality of the pain for each type of arthroscopic treatment. The major pain experienced during injection of anesthetics and major pain experienced during surgery were noted and compared. Intra-operative side effects such as nausea, vomiting, bradycardia, and hypotension and duration of surgery were recorded. After the surgery postoperative pain using the VAS values was recorded at time intervals of 2, 5, 9, 12, 16 and 24 hours. Patients were asked if they would like to have any future arthroscopic knee procedures under local anesthesia and the degree of overall satisfaction (not satisfied, satisfied, very satisfied) was recorded. When patients complained of pain (VAS score  $\geq 4$ ), 75mg of diclofenac were given orally as a rescue medication. Duration of effective analgesia measured since the time of surgery completion to the first requirement of rescue analgesia was noted.

For the statistical analysis of the data, SPSS 12.0 software was used. Data were expressed as mean  $\pm$  standard deviation. Group comparison was performed with t test (Student) determining a statistically significant difference between examined groups and p value  $< 0.05$  was considered statistically significant.

## Results

There was no significant difference in demographic data of the patients in groups regarding age and gender distribution. The mean patients' age was  $26.2 \pm 11.5$  years in group B and  $28.9 \pm 14.3$  years in group BM (p=0.45). Each group had 9 male and 3 female patients. The mean duration of arthroscopic surgery was  $25 \pm 8$  minutes in patients from group B and  $27 \pm 10$  minutes in

those from group BM, without a significant difference between the groups (p=0.75). There was no significant difference in mean VAS pain scores between the groups during the injection of anesthetic (p=0.885) as well as during the surgical procedure itself (p=0.817) (Table 1).

Table 1. Mean pain level (VAS values) in patients from bupivacaine (B) and bupivacaine plus morphine (BM) group during anesthetic injection and arthroscopic surgical procedure conduction

Mean VAS values mean ± std	Group B	Group BM	P value
Anesthetic injection	5.92 ± 1.44	5.83± 1.34	P=0.885
Surgical procedure	3.25 ± 1.82	3.08 ± 1.68	P=0.817

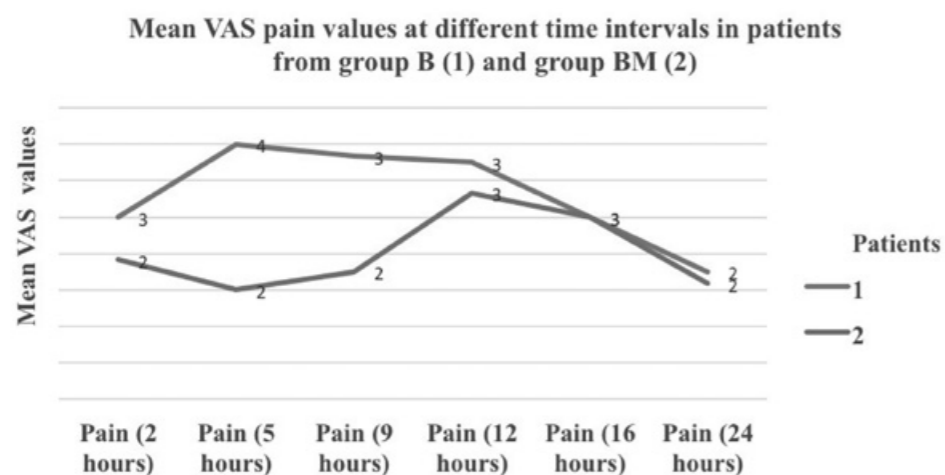
Common mean VAS pain value for both groups was significantly higher during the injection of anesthetic than during the arthroscopic surgical procedure itself (p < 0.001) (Table2).

Table 2. Mean pain level (VAS values) in patients from both (B and BM) groups during anesthetic injection and arthroscopic surgical procedure conduction

Mean VAS values mean ± Std	Group B Group BM	P value
Anesthetic injection	5.88 ± 1.36	
Surgical procedure	3.17 ± 1.71	P < 0.001

The VAS pain values were determined 2, 5, 9, 12, 16 and 24 hours after the surgery. Results showed that patients from group B had significantly higher VAS values after 5 (p=0.000) and after 9 hours from the surgery (p=0.02). There was no significant difference in the VAS pain values between the groups after 2 (p=0.248), after 12 (p=0.513), after 16 (p=1) and after 24 (p=0.167) hours from the surgery (Figure 1).

Figure 1. Mean pain level (VAS values) at different time intervals after the completed arthroscopic surgical procedure in patients from bupivacaine (B) and bupivacaine plus morphine (BM) group.



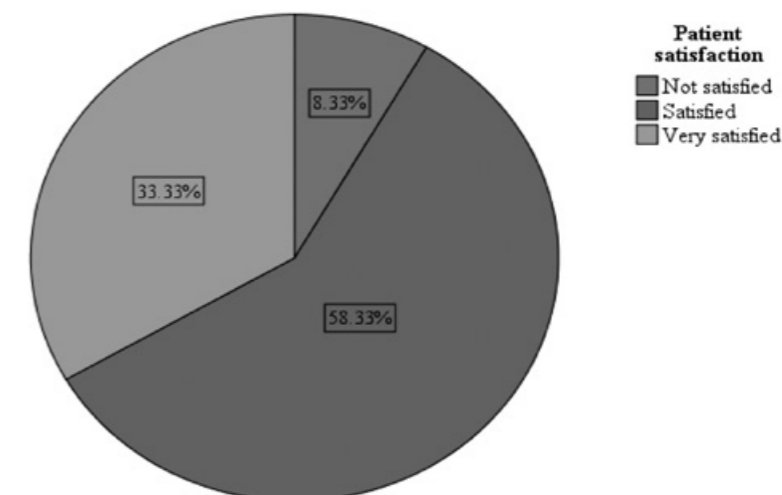
According to the results (Table 3), the time from surgery completion to the first requirement of rescue analgesia was significantly longer in patients from group BM compared to those from group B (p=0.012).

Table 3. Mean time (hours) for rescue analgesia in patients from bupivacaine (B) and bupivacaine plus morphine (BM) group

Mean time for rescue analgesia	Group B	Group BM	P value
Time (hours)	7.83 ± 3.35	12.0 ± 4.07	P=0.012

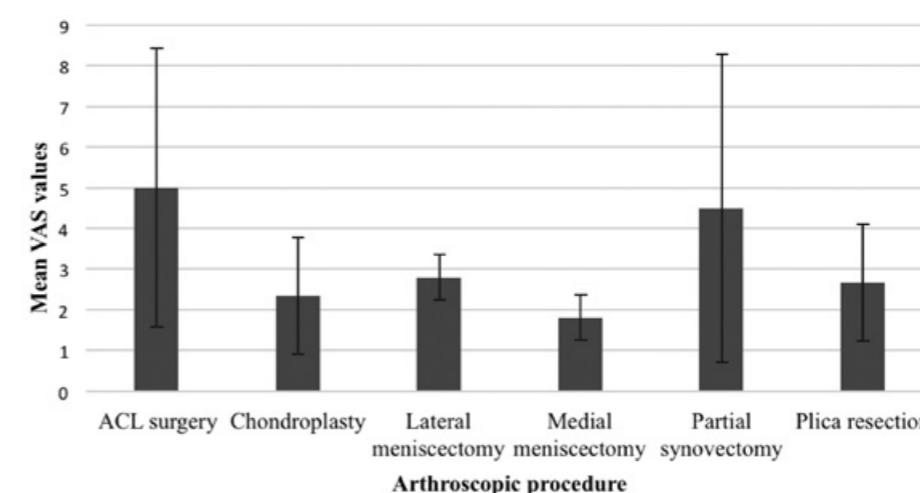
There was no significant difference between the patients from the studied groups regarding their subjective satisfaction. In both groups there were 4 very satisfied, 7 satisfied and 1 not satisfied patient. The common results for both groups showed that 33.33% of the included patients were very satisfied, 58.33% were satisfied and 8.33% of the patients were not satisfied with the performed knee arthroscopy under local anesthesia (Figure 2).

Figure 2. Patients satisfaction at final follow-up in patients from both (B and BM) groups.



Considering the intra-operative pain experienced during different arthroscopic procedures, the results showed higher VAS pain values (≥ 4) in ACL surgery and partial synovectomy than in plica resection, chondroplasty and medial and lateral meniscectomy (Figure 3).

Figure 3. Intra-operative mean pain level (VAS values) experienced during different arthroscopic procedures in patients from both (B and BM) groups.



One patient from group B and one from group BM had nausea and vomiting. Other side effects were not presented.

## Discussion

Local anesthesia for knee arthroscopy has recently become more popular because it offers several advantages, such as decreased hospital and recovery time, low cost, rare side effects and complications that are seen in spinal and general anesthesia and prolonged post-operative analgesia.

For successful arthroscopic surgery under local anesthesia, the right anesthetic choice is very important. The most of the authors agreed that chondrotoxic effects increased from ropivacaine to mepivacaine to bupivacaine to lidocaine in a time-dependent and concentration-dependent manner, which means that a longer exposure to a higher concentration of local anesthetic, such as with a pain pump, should be avoided (14-20). The study by Grisko showed that exposure of primary human chondrocytes to a 2% concentration of lidocaine caused massive necrosis of chondrocytes after twenty-four hours, 1% lidocaine and 0.5% bupivacaine caused a detectable, but not significant decrease in viability after twenty-four hours, while 0.5% lidocaine, 0.25% bupivacaine, and both concentrations of ropivacaine (0.5% and 0.2%) did not affect chondrocyte viability (21). According to the study the lowest anesthetic concentration with a less chondrotoxic and good analgesic potency should be chosen (21).

Aiming to decrease the necessary concentration of a local anesthetic because of the chondrotoxic effect and to prolong the post-operative analgesic times of local anesthetics after knee arthroscopy, some opioids (morphine, fentanyl) are administered intra-articularly in combination with local anesthetics. Some authors demonstrated that morphine can provide a later onset of analgesic peak action at 3–6 h, and pain relief up to 24 hours without causing gross chondrotoxicity (17, 25, 26, 28, 29, 30). According to some studies a poor lipid solubility of morphine hampers its passage across the synovial membrane into the blood stream and increases the drug duration (31). The study by Brandsson showed that the systemic absorption of the injected morphine was very low in the joint and that its analgesic effect on the joint was due to the existence of peripheral mechanism in the joint, which reduced the pain without a significant systemic effect (32). Although a relatively wide range of intra-articular morphine doses (1mg to 15mg) were used in the studies, the dose dependent manner in morphine analgesic effects and dose dependent side effects from morphine are still not clear. The studies by Kalso, Kanbak and Likar showed that 4 to 5mg of intra-articular morphine was more effective in reducing pain than 1mg of intra-articular morphine (33-35). The study by Yari showed that 15mg of intra-articular morphine was more effective in reducing pain than 4 to 5mg at 4, 6 and 24 hours after knee arthroscopic surgery (36). Opposite to them Stein *et al.* reported effective analgesia after knee arthroscopy with 1mg morphine and Drosos *et al.* failed to detect any significant differences in pain scores among the groups who received 5 and 15mg of intra-articular morphine (24, 25).

Currently, bupivacaine and morphine are widely used in combination to provide effective analgesia. Although the most of the authors have shown that this combination can provide effective pain relief in patients undergoing knee arthroscopy, there are also authors that negate it (30, 37 -41). Karlsson *et al.* reported significantly lower pain scores in the morphine group

at 24 and 48 h and in the bupivacaine group at 2, 4 and 6 h after knee arthroscopy (30). In the group that received a combination of both bupivacaine and morphine, the pain scores were significantly reduced throughout the whole postoperative observation period without side-effects or complications from therapy in any of the groups. Opposite to this study, De Andreas *et al.* reported that analgesic efficacy of morphine-bupivacaine mixture was not more efficacious than bupivacaine or morphine alone (40).

In our study we compared the results in patients where knee arthroscopy under local anesthesia was performed using either 20ml of 0.5% bupivacaine with adrenaline or 10ml of 0.5% bupivacaine with adrenaline plus 4mg morphine for intra-articular application. Calculating that median synovial fluid volume in the knee joint is 3.05ml, the final concentration of bupivacaine was 0.43% in patients from group B and 0.32% in those from group BM (42). We wanted to determine if lower concentration of bupivacaine combined with morphine is effective as higher concentration of bupivacaine for local anesthesia in patients where knee arthroscopy was performed.

The obtained results showed that there was no significant difference in the presented pain between the patients from group B and those from group BM during the injection of the anesthetic agent, as well as during the surgical procedure itself, which means that both bupivacaine and bupivacaine plus morphine solution are equally effective obtaining the same level of analgesia during the knee arthroscopy. Injection of the local anesthetic was the most painful phase of the entire procedure according to our results. Our results corresponded to the results published by Takahashi *et al.* (43). We found that a local anesthesia provided good pain control during partial meniscus resection, chondroplasty and plica resection, but partial synovectomy, especially in the suprapatellar pouch, anterior cruciate ligament (ACL) residual remnant resection, subtotal meniscectomy and chondroplasty which included micro-fracture of femoral condyle, were painful in some patients. Our results in general corresponded with the results presented by Takahashi and Dye who demonstrated that severe pain was reported during probing of the suprapatellar capsule, meniscal capsular margin, infrapatellar fat pad, and the insertion site of the cruciate ligament (43, 44). Regarding the postoperative pain, our results showed significantly lower VAS pain values in patients from group BM after 5 and after 9 hours from the surgery. A significant difference in VAS values was not found after 2, 12, 16 and 24 hours. The time for rescue analgesia with 75mg of diclofenac because of knee pain (VAS  $\geq$  4) was significantly longer in patients from group BM than in those from group B. Because the mean time for rescue analgesia was  $7.83 \pm 3.35$  hours in patients from group B, it is our opinion that diclofenac uptake and its analgesic effect influenced the similar pain level in both groups after 12 hours from the surgery. Our results corresponded to those presented by Karlsson, Allen, Yang, and Joshi, and were opposite to those by De Andreas and Bjornsson (30, 37-41).

We found only mild side effects (nausea, vomiting) in 2 patients without a significant difference between the patients from the investigated groups. There were no patients in whom due pain and discomfort during the surgery conversion to general anesthesia was conducted. Thus,

more than 91% of the included patients were either satisfied or very satisfied with their anesthesia and agreed to have the same procedure performed under local anesthesia in the future. There was no significant difference regarding the patients' subjective satisfaction between the studied groups. Our results corresponded to the results from other studies (12, 45).

The small number of patients with a weak statistical significance was the first disadvantage of our study. Group heterogeneity according to the different arthroscopically treated knee disorders with different pain level, was the second disadvantage of our study. Grouping of the patients according to the type of arthroscopic surgery as previously done by Marchal *et al.* could optimize the study sensitivity (46).

**In Conclusion** - a solution of bupivacaine plus morphine is more effective than a solution of higher concentration of bupivacaine by providing better post-operative pain relief with reduced need for supplementary analgesics and by lengthening the time interval for rescue analgesia, all with minimal and similar side effects. This is very important considering chondrotoxicity of higher concentrations of bupivacaine.

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## THE HISTORY OF MECHANICAL VENTILATION IN MACEDONIAN ANESTHESIOLOGY PRACTICE

*Andonov V<sup>1</sup>, Sholjakova M<sup>1</sup>, Nikolova-Todorova Z<sup>2</sup>, Nojkov J<sup>1</sup>, Shosholcheva M<sup>3</sup>*

<sup>1</sup> *Free researcher at Ss. Cyril and Methodius University, Faculty of Medicine, Skopje, Republic of North Macedonia*

<sup>2</sup> *International Eye Hospital, Skopje, Republic of North Macedonia*

<sup>3</sup> *University Clinic of Surgery "St. Naum Ohridski", Skopje, Republic of North Macedonia*

### ABSTRACT

In the era of the infection with a new Coronavirus, 2019-n CoV, the mechanical ventilation (MV) becomes one of the topics that are in the focus of attention. The aim of this paper is to present historical data at the beginning, development and progress of MV in the Macedonian anesthesiology practice. The text is divided in several parts concerning the history of mechanical ventilation in the world; the use and classification of ventilators and ventilator modes; as well as the Macedonian experience with MV, with a focus on education.

The development of the technology offers new types of more sophisticated machines which are adapted to the needs of the patients, which permits the patients easier to coop the mechanical ventilation.

In conclusion, the authors emphasize the importance of MV as a sophisticated doctrine with a need for constant education and frequent refreshment of the knowledge.

**Key Words:** *ICU, mechanical ventilation, modes of ventilation, ventilators.*

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## Introduction

With the beginning of the year 2020, the world was confronted with an unexpected spread of a disease caused by an infection with a new Coronavirus, 2019-n CoV, which is manifested as a difficult form of viral pneumonia and acute respiratory distress syndrome (ARDS). The infection took the globe's dimensions and on March 11<sup>th</sup> 2020 the WHO announced that it is an emergency of the globe – pandemic (1). The disease ultimately entered in our country. While waiting for different guidelines about the management and treatment of those patients, our country had several challenges: to audit our health care capacities for acceptance of great number of patients, the ability of the professionals to cope with difficult forms of lung failure due to 2019-n CoV, and the capacities of our Intensive Care Units (ICU) and availability of ventilators (2).

The present fear of an unknown illness with all its forms, made the Macedonian anesthesiologists to gather on one platform from which they absorbed the knowledge, information about the forms of the illness, guidelines for treatment and exchange of experiences with colleagues all over the world.

The main clinical manifestations of the illness caused by Coronavirus, 2019-nCoV were failure in the oxidative processes, hypoxemia with decreased values of the respiratory index, development of ARDS, shock, multiple organ failure, disturbances in coagulation and others. It was obvious that the use of respiratory machines will be an ultimate measure (3,4,5).

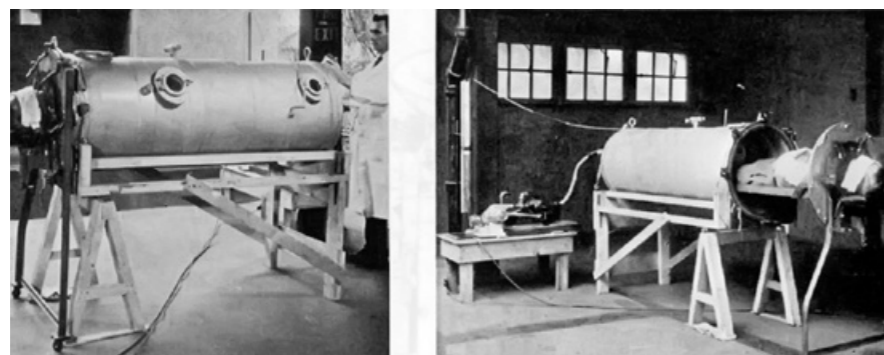
As follow up, mechanical ventilation became the main tool for treatment of all critical care patients. Its indications expanded, especially for the patients with respiratory failure.

## The History of the Development of the Mechanical Ventilation

The roots of the historical development of mechanical ventilation in the world took place in the middle centuries, when Andreas Vesalius (1543) described that lungs in animals could be ventilated with a tube in trachea and a balloon for inflation with air (6). But the real start of the mechanical ventilation was in 1907, when Heinrich Dräger, described a new technology for ventilation with the “insufflations of fresh air in the lungs” (7).

Different versions of ventilators for mechanical ventilation, as noninvasive machines driven on negative pressure were developed prior to the introduction of the “iron lung” (6).

*Figure 1. Iron lung ventilator*



*(negative pressure in the abdomen, lungs and the chests)  
From: <https://mechanicalventilation.weebly.com/index.html>*

The “iron lung” was developed in the beginning of 20<sup>th</sup> century, constructed by Phillip Drinker in 1928 and known as Drinker's ventilator (First generation), and it worked on negative ventilation mechanism. Later, it was improved by John Haven Emerson (1931) and Both (1937). Over the time the need for ventilators increased and from this group of noninvasive ventilators the Biphasic Cuirass Ventilators were introduced and widely used during the great poliomyelitis epidemics (8). Still, despite these type of ventilators did not meet the optimal needs for artificial ventilation; they were used until 1970's.

After the Second World War, a mechanical assistant for anesthesia was developed by John Haven Emerson in 1949. The need for ventilation assistance during anesthesia increased with the use of muscle relaxants, so the anesthesiologists started to use manual ventilators (9).

In August 1952, during the poliomyelitis epidemics in Denmark, the Blagdam Hospital in Copenhagen was confronted with enormous number of cases with bulbar paralyse. Before that event, the mechanical ventilation was achieved with “iron lung”, but this crisis caused the need of introducing new way of ventilation with positive pressure. The main focus was to the prototype of Safar's mask-bag ventilator which had positive effects on ventilation and survival rate of the patients (second generation ventilators).

Bjorn Ibsen and other authorities in Denmark accepted with consensus the use of simple bag-ventilators which were used by volunteers; the students, nurses and others for hours of manual ventilation of the polio victims. It was clear that hundreds of patients had the need for artificial ventilation. The mission was a success, which decreased the mortality ratio for 3.1% from the total number of resuscitated patients (10). This unknown fact is the real beginning of the intensive care treatment and the use of ventilators out of the operating theater; what is very similar to the actual situation with the COVID-19 virus.

After this period, in parallel with the technological developments, there was ongoing process of development of the ventilators for the anesthetic machines in ICU. Respiratory machines from different firms like Dräger, Engström, Puritan Bennett, Siemens, Hamilton and others were present on the market (9).

## Types of Ventilators

Mechanical ventilation (MV) is a supportive, not curative, method of treatment in many ICUs. In general, from the introduction of ventilators in clinical practice up today, they are classified through the development of different types of drives.

MV in the literature is named with the synonymous as Positive Pressure Ventilation (PPV) or Intermittent Positive Pressure Ventilation (IPPV) since its main function is the respiratory support by lungs inflation with using positive pressure ventilation.

The decision for applying MV depends on many factors, but it is always crucial and it must be taken into account, that no model of MV could cure the main illness. For the patient's treatment and its outcome, the most important is the type of the disease; whether it is curable or not? MV

is only a support for better oxygenation until the body defeats the illness, or more precisely its main goal of use is **prophylaxis of other organs decompensation** (11).

The main **indications** for use of ventilators are different types of respiratory failure from ventilatory or hypoxemic origins, and the development of an apnea or acute respiratory failure (ARF) are the standard criteria for use of MV (12).

Kazmark R.M in 2011 made a simple classification of different types of ventilators according to the year of their appearances in the practice (8). (Table 1.)

**Table 1.** Classification of the ventilators used in ICU by the time of development

- <b>Negative pressure ventilators</b> , 19th - 20th century: "tank ventilator"			
- <b>Noninvasive positive pressure ventilators (NIV):</b> a bag and mask manual ventilator (1887) - Dräger's Pulmotor (1911); Benet TV, Bird Mark series; <b>Current new devices:</b> Respirtronics STD or V60; Dräger Carina, Respritonics Vision, Sullivan VPAP; The first version of the Oxylog® ventilation device			
- <b>Invasive positive pressure ventilators:</b> Suitable for <b>long respiratory support in ICU;</b>			
Generation	Period of use	Main characteristics	Commercially available
First	1940-1970	Volume control ventilation; No trigger; no PEEP	Morch, Engström, Emerson; Dräger Assistor 642 (1966); Bird Mark 4 and 8
Second	1970-1980	Patient triggered inspiration; incorporated extensive alarms and monitors, IMV	Puritan Bennett MA-1, Siemens Servo900C; Ohio 560; Manley 1-V; Dräger Spiromats 661
Third	1980- 1990	Microprocessors control; Meet the patient's demand; Flow trigger, PCV, VCV&SIMV.	Dräger UV-1; UV-2; Puritan Bennett 7200, Bear 1000, Servo 300, and the Hamilton Veolar
Fourth	1990 –to day	Electronic modifications, multiple forms of ventilation; closed-loop control; Faster weaning; NIV;NIPPV with helmets	Dräger Evita V300 и Evita V500; Baby log 8000, Dräger Savina; Puritan Bennett; Hamilton; Bird new genera- tion; Smart Care/PS
Future	2020 - future	Let's see	

(by Kacmarek RM 2011)

**Legend:** (NIV- noninvasive ventilation; PEEP-positive end expiratory pressure ; IMV-intermittent mandatory ventilation ; PCV- pressure control ventilation ; VCV-volume control ventilation; SIMV- synchronous intermittent mandatory ventilation; NIPPV- noninvasive positive pressure ventilation)

### Development of Ventilation Modes

The very early forms of ventilation machines were only pumps which supported ventilation ("air pumps"). Later with the technological development the ventilators were improved and they became the tools adapted to the patients' needs. Its improvement was in a close relation

with the development of different modes of ventilation appropriate to the state of the patient and his lungs (13). With the introduction of AutoFlow, the free ventilation and the proportional pressure support of ventilation were automatically adapted to the changes in the lungs and the physiology of respiration (14).

The noninvasive ventilation (NIV) again became very useful, especially noninvasive ventilation with positive pressure (NIPPV) including CPAP and Bi-level Positive Airway Pressure (BiPAP) with helmets (Helmet-based ventilation) with possibilities of use of all modes of ventilation. They also became the solution for treatment of critical patients infected with COVID-19 virus (15, 16).

### Macedonian Anesthesiologists and Mechanical Ventilation from the Beginning until Today

After the Second World War, in 1947 the Medical school at the University "Ss Cyril and Methodius" was established, in Skopje, which became the leader of the medical science and development in the country. The Surgical Clinic, as a part of the Medical Faculty was the bearer of the education in the field of anesthesiology, with development of resuscitation and artificial ventilation, as well as rapid progress in development of the intensive care unit (17).

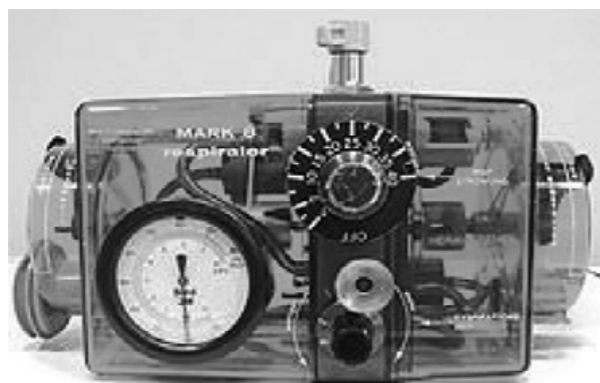
It is very important to notice that though artificial ventilation was strongly linked to the general anesthesia practice, still in the 1960, the first two ventilators in the country were brought, to the Infective Clinic in Skopje. Those were two ventilators known as "iron lungs", donated through the program of the United Nations UNRRA (United Relief and Rehabilitation Administration). The ventilator "iron lung" was robust, and it took a lot of space in the room, but unfortunately it was not used at all; even though in that period in the R. of Macedonia the epidemic of poliomyelitis with many cases was also present, which caused invalidity among many patients some of whom died because of bulbar paralysis.

The first room for Intensive Care in the Republic of North Macedonia (RNM) is opened in 1955 as a part of the Surgical Clinic in Skopje. This was dictated by the needs of the postoperative care of the surgical patients, particularly after heart surgery. It was the start of the cardiac surgery in Skopje. Surgeons operated „off pump" patients with mitral stenosis which in that time was very frequent, because of the present streptococci's anginas, or patients with pericarditis caused by tuberculosis'.

The first, proper Intensive Care Unit (ICU) was established in 1961 at the Department of Anesthesiology as a part of the Clinic of Surgery at Medical Faculty in Skopje, in very simple conditions, in a large room, where critically ill patients were located in a status of shock. The room was very poorly equipped; there were only devices for fluid therapy, oxygen supplement and defibrillator. In 1965, the "Central gases supply system" was introduced in the operating theaters and in the ICU, which was the first improvement in equipment in this department. Very soon after, in 1967 the first Manley's ventilator from UK was obtained (second generation), with primary aim to be used for controlled ventilation in anesthesia, though, because of the lack in

equipment, it was used in the ICU. According to the needs, at the end of 1968 two Spiromats Dräger were supplied (second generation). This was also period when the new ICU-s in the Military hospital in Skopje and in the City Hospitals in Skopje, Bitola and Shtip were opened.

*Figure 2. A bird Mark 8 ventilator has been modified by a time cycled servo mechanism to function as an inexpensive ventilator with high peak pressure capabilities. This system was designed to deliver IMV-PEEP therapy at levels not usually available on commercial ventilators. Crit Care Med May-Jun 1978; 6(3):185-8.*



In 1984, the ICU of the surgical Clinic in Skopje was supplied with two ventilators, Bird Mark 8 (Fig 2.) for ICU and mark 4, for anesthesia (third generation) (9,17).

In the eighties of the past century the Dräger ventilators UV-2 (UV-universal ventilator) were very popular, and in the first half of the 1980<sup>th</sup>, two of them were procured for the ICU of the Surgical Clinic in Skopje. In this period open heart cardiac surgery started and for this purpose a Narcoso-spiromat Dräger 650 and one additional Ventilator UV-2 were supplied. Those machines allowed better control of the desired parameters of the artificial ventilation (7), more possibilities for assisted ventilation with trigger, more modalities of ventilation (PEEP) etc.

During this period intensive care units of other clinics were also developed (cardiology, nephrology, and pulmonology) including the pediatric ICU, where there was increased need for artificial ventilation. Cardiology and pediatric ICUs were also supplied with two ventilators UV-2 (Dräger), while pulmonology and nephrology were equipped with a Spiromats Dräger.

In 1990, the new additional department of the Surgical Clinics was built and the Department of Anesthesia was transformed and renamed in the Clinic for Anesthesia, Reanimation and Intensive Care (KARIL) in the scope of the Medical school in Skopje. In this period the procurement of the new built ICU was supported by an aid from the German's Red Cross. The new ICU was supplied with 6 ventilators Siemens servo 900 D (third generation) and other devices as 15 monitors (ECG, P/min, NIBP, pO<sub>2</sub>, with central station and other supplies as aspirators, drainage's pumps, portable X-Ray and two mobile ventilators). For the new operating theaters 15 anesthetic machines were procured with ventilators (Siemens) and two anesthetic machines Servo Ventilator's 900C with the ability for artificial ventilation. A mobile ventilator – Oxylog® was supplied also for the new Emergency department in the surgical Clinics, who served for transport of patients (third generation) and the same provided ventilation with constant volume.

### The First Attempt for Our Own Ventilators Named 2XA

In the 1989 and 1990, Prof. Vladimir N. Andonov, in collaboration with the electro-engineer eng. Jovan Andonov, had constructed three prototypes of transistor's ventilator. In the beginning of 1990 Federal comity for patents in Belgrade, put them in probe function and demonstrated in the Hospital "Dragisha Mishovich" in Belgrade. They were used as probe in 75 patients during anesthesia in neurosurgery working constantly well about 9 days.

The Authors got the Certificate of use for the ventilator; and during the 1990-1991 two of them were constantly used in the operating theaters. Later they were substituted by new sophisticated ventilators.

### The New Era of Ventilators

The modernizations of equipment continued and in the last 20 years the most sophisticated ventilators of the third and fourth generation were obtained, such as 7 apparatus Dräger Evita 4 in 2010 and later additional two in 2012, two -Maquet Servo 1 in 2008 and 2010 and four Puritan Bennett, in 2009 two and two in 2010; and the accessories like a mobile ventilator Dräger in 2008, a Bronchoscope and a set for video-intubation in 2019.

This was the basis for the introduction of optimal conditions for care of patients on MV. The nursing of the patients on ventilators was also a complex process, which included several pre-conditions and skills, in order to decrease the incidence of complications. This aim was reached by the staff of ICU in KARIL by using adequate hygienic measures and some aseptic techniques which among other needed good humidifiers of the gases, which were developed in parallel with the new generations of ventilators (18). In addition, the personal sets for each patient, including aspirators, sets for closed techniques of aspiration, adequate space between the patients, and educated staff were the pre requisites for a successful nursing (11).

The basic need for care of the patients on MV were the concerns regarding the positioning of the patients (head elevated on 45 degrees), the possibilities for prone positioning, measures for stress ulcer prevention, care for/ and stimulation of the bowel motility, and prevention of deep veins thrombosis. The care for the metabolic needs of the patients on ventilator, ordered further improvement of the knowledge and development of the parenteral nutrition and immune-nutrition of those patients. Constantly and dynamically, according to the Euro – guidelines, in the ICU of KARIL the methods for early enteric nutrition were used, with several techniques for selective decontamination of the digestive tract.

Looking from the historical distance, the entrances in the new ICU in 1993, the separation of the neurosurgical patients in the new neurosurgical ICU (2000), and the introduction of the pediatric surgical ICU (2012), were the crucial dates of constant development and improvement of the quality and outcomes of the patients on MV. The measurable parameters were in everyday progress, the duration on MV was decreased, the numbers of early weaning with re-intubation, the appearance of ventilator induced pneumonia, atelectasis and other complications became rare as well.



It must be emphasized, that very often the ICU of KARIL which was surgical ICU, started to take care of critical patients from the other Clinics like internal medicine, neurology, pediatrics, infective disease and others. Some of those patients required prolonged MV, up to three years, because of neural degenerative diseases.

**Figure 3.** Modern NPPV: Philips Respironics V60



This is an extremely long period for hospital care, and it is an indicator of the successful care of the patient's somatic status. It must be noticed that they were the first two patients in the RNM, who were discharged from the ICU of KARIL to "home MV care". In addition, the patient's families were educated how to maintain, clean and use "Home ventilator" properly.

#### **Establishment of the ICU in Neurosurgery**

After the moving of the ICU of KARIL in the new building (1993), the space where was the old ICU in the old building (already equipped with the central gases system) was adequate for opening a new ICU with 9 beds for the need of neurosurgery and plastic surgery. Very soon, a part of the educated staff from the ICU in KARIL was disposed in this ICU and a part of the old ventilators were used. Consequently in September 2000 the neurosurgical ICU was opened. It possessed three „Evita 2 Dura“ ventilators Dräger, and two ventilators “Siemens 3000“, one Oxylog, monitors, aspirators and vacuum pumps. In 2009 two ventilators Dräger - „Savina“, and one Oxylog were obtained, with Ministry of Health donating an additional ventilator „Evita 4“- Dräger. In the 2019, after the last renovation of this Neurosurgical Intensive Care Unit (NICU) the old ventilators were substituted with 10 new modern ventilators „Savina 3000“, one Oxylog, 11 monitors with central monitoring station, and 6 of them had the possibility for invasive parameters measurement.

#### **The Development of the Intensive Care Units in the Other Hospitals in RNM**

The rest of the Hospitals in the Republic of North Macedonia also followed the new trends for opening an ICU as a part of the operation tracts. Since the main criteria for admitting the patients in the ICU were the presence of severe respiratory failure among the patients, it was reasonable

that the crucial role in those ICUs to be played by the anesthesiologists. Beside the Medical school in Skopje, the bears of this activity were the Military Hospital and the City Surgical Hospital in Skopje, and the hospitals in the other cities, primary in Bitola, which were part of the Regional Medical Centers.

In 1971, the Military hospital in Skopje started to operate in a new facility, so they become able to start to work in the field of critical care, according to modern principles of a medical care. Modern department of Intensive Care was opened, with the central gas systems and supplied with ventilators. The first ventilators were Bird mark, and Dräger ventilators. In that period the German firm Dräger had the monopole in supplying the apparatus for anesthesia and ventilators in the whole country (Ex Yugoslavia). It was a doctrine coming from the ex Yugoslav People's Army aiming to unify this activity, as highly important for military and others special situations, but also to easily supply the spare parts and servicing. This was the reason the factory for medical instruments “Instrumentalia Zagreb“ in collaboration with the firm Dräger to start the production of the “home” apparatus for anesthesia “Sutjeska”, and the firm “Jugomontana” from Belgrade to perform all installations for central gas systems in the country. In addition to this, the Field's military hospitals had also Dräger's portable machines for anesthesia, packed in two wooden boxes which were transportable on horses.

The City Surgical Clinic “St. Naum Ohridski” in Skopje, took also, a very important part in the development of the Intensive care in our country. The first generation of anesthesiologists started to work in the early 60s from the last century. Some of them were engaged in Denmark in the period after the big epidemic of polio with 4 others doctors from RNM. That was an opportunity the experiences with mechanical ventilation to be transferred back in the country.

In 1968 in this Hospital the surgical ICU with 8 beds was opened and was procured the first ventilator “Dräger respirator EB 800 0” (EV 800) and a separate machine which possessed the oxygen tent. Central gas system was installed in 1970. Later on, in 1988 two ventilators Evita Dräger were obtained. In the same year, graces to a donation from Japan, the 4 ventilators “Acoma” were brought. In 2000 the ventilator Evita Dräger Dura 4 was bought. In the 2011, with a decision from the Ministry of Health for modernization of the medical sectors, the Hospital was obtained with three ventilators Dräger Evita 4 with compressors.

The beginning of the ICU in Bitola dated since 1963 when the government of Ex Yu issued a decision to build new military hospitals in Belgrade, Skopje, Split, Ljubljana and a new general Hospital in Bitola. It was a very modern hospital with central gas installed system and department of ICU with 6 beds, 6 monitors with central station, defibrillator, and two ventilators “Spiromats Dräger”.

Other Hospitals in the Country with ICUs introduced were the Regional Centers in Shtip, Veles, Ohrid, and Tetovo, and then Strumica, Gostivar and Gevgelija. The units were obtained in the period from 1975-1980, having been equipped with monitors, defibrillators and ventilators. The first monitors brought in the country were made by General electric.

In the past, the largest quantities of imported ventilators in the country were Dräger Assistor 641. Those machines were produced by Dräger between 1960-1975, but they came in our country in the beginning of eighties.

They were positive pressure cycled machines, very noisy and there was high risk for barotraumas. The only ability was the possibility for regulation of the frequency of ventilation, the maximal inspiratory pressure and the percentage of oxygen in the respiratory mixture. They were very crude and difficult for the patients and could have been used only if they were in deep coma. That is why it was necessary to use deep sedation or relaxation of the muscles with curare, which was only valuable in this time beside the suxamethonium. The later versions of ventilators were from the series 'Spiromats' which were more sophisticated, working on electrical power, with the possibilities for assisted ventilation and PEEP.

### Education for Mechanical Ventilation

The theoretical, but much more learning by practical doing, are the main components and prerequisites for successful use of the MV. In the very beginning, the use of MV was accompanied with high mortality, since in general the ventilated patients were in deep coma, or in terminal state. As time passed, and the experience increased, the staff became more skilled, the indications for MV were wider and the mortality started to decrease.

Nowadays, the knowledge and the training of the doctors of many specialties with ICU are much improved. The reason of that is the modern approach of the learning process of the trainees, the continuing medical education for the specialists of anesthesia and the intensive collaboration with the colleagues from the other specialties.

The curriculum of specialization of anesthesia and Intensive care is updated according to the Euro - ESA guidelines, which requires: 60 months specialization, with 150 hours of theoretical lessons on basically sciences, pulmonology, machines and MV, with 22 months practical work in intensive care and emergency department, including ICUs in pediatrics, cardiology, pulmonology, and nephrology, and the practice in transfusion medicine and the X-Ray institute. This is a solid base for a successful use of MV (19). In addition, the most of the nurses working in the ICU are educated at the faculty for nurses, but there is a lack of specialized ICU nurses. There is also the need for respiratory physiotherapists, which today in the era of Corona V-19 Virus infection became the most important persons for successful weaning from MV (20).

The role of the anesthesiologists was also in educating specialists from the other areas of medicine which require a basic knowledge of MV. We would like to note that some specialists in cardiology were educated for performing endotracheal intubation, the colleagues from the Pediatric Clinic as well, after their prime education for ICU abroad, were in a short rotation in ICU in KARIL. The ICU in the Infective Clinic was opened under the supervision of the anesthesiologists, and their staff was educated and practiced for the use of MV with the help of the anesthesiologists. We are aware that many professionals from the other specialties, who

are incorporated in the ICU, had not the sufficient practical knowledge for the use of MV. We speculate that this is result of the small number of the patients with the indication for MV. In our opinion, there is a need for revision of their programs for specialization, where the theoretical lessons should be substituted with practice. The anesthesiologists are proud for the long lasting cooperation with some institutions, such as with the Institute for Transfusion medicine, with the Clinic of nephrology, Clinic of neurology and the Clinic of pulmonology. And in the end we would like to mention the cooperation with the colleagues from the Infective Clinic, where anesthesiologists together with the infectologists, took eminent place in the faith on saving the patients ill from the Corona V-19 Virus.

### Conclusion

With this presentation the authors of this article had the goal to inform the public with the historical data about the use of the mechanical ventilation in the RNM, and for the types of ventilators which were used in the past. From the text above, it can be concluded that the use of ventilators for MV is a sophisticated doctrine which needs constant education and frequent refreshment of knowledge. The development of the technology offers new types of more sophisticated machines which are adapted to the needs of the patients and enable the patients to cope much easier with mechanical ventilation.

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**Limitation:** There are only few written data about the development of the anesthesiology and the intensive care in the RNM. The recent information is a result of the memories of the authors of this text and the persons mentioned above. Also, the old machines are destroyed or sold, so the enclosed images are from the internet.

**Conflict of Interest:** The authors not referred any conflict of interest.

**Contribution:** All authors took the equal part in the realization of this article.

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The guidelines for authors adhere to the uniform Requirements for Manuscripts submitted to Biomedical Journals: [www.nlm.nih.gov](http://www.nlm.nih.gov).

**Language and style** of the manuscripts should be clear, simple to according the language, anesthesiological and medical taxonomy.

The manuscript has to be written in **English Manuscripts** should be written in **Microsoft Word** (\*.doc format) with **Times New Roman** font and **size 12**. Margins on left, up and bottom should be 3 cm and right margin should be 2,5 cm.

The inline space should be 2. Do not use Bold or Italic letters for the whole text (only for parts that have to be emphasized). Manuscript should not exceed 10 pages (without the references).

**Abbreviations and correct medical terms** should be used according to the International Committee of Editors of Medical Journals (<http://www.icmje.org>). Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers. Avoid abbreviations in the title of the manuscript. The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

### **MANUSCRIPT SECTIONS**

- Manuscript should be organized in:
- Title page
- Text organized in IMRaD
- Acknowledgments
- Authors Contribution
- References

Review articles, case reports, therapeutic and technological innovation, discussions, critics, impressions from meetings, information for international conferences and reviews of new books or variate may be written in different sequences and manners.

### **TITLE PAGE**

**The title** of the manuscript written in CAPITAL LETTERS.

**Authors Surname and Name initial** (Jovanov J, maximum 6 authors), without academic or other titles.

**Name and address of the institution** where the authors come from whit the subscribed digits

**Abstract in English.** Abstract should include up to 250 words and should contain goals of the paper, important elements from the methodology, concisely displayed results and conclusion. Each abstract at the end must have **Key words:** in alphabetical order.

### **TEXT**

- Introduction,
- Matherial and Method,
- Results
- Discussion
- Conclusion

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**Introduction** section should include a literature overview in relevance to the elaborated problem. In this sections 3-5 key references are cited and this section should not be longer than 2 pages.

**Material and method** sections includes detailed description of the performances in the research as well as the statistical analyses used. This section should include: time during what the research was conducted, type of the study, place of where the research was undertaken, randomization or stratification used (clear description of the examined groups), exclusion and inclusion criteria, method, analysis types, apparatus and instruments used and referent values of the examined features (in SI-International System units).

**Results** are displayed in simple manner with text, images, tables and charts that are submitted in the text where author wants to stand, titled and numbered appropriately. Additionally, on separate document all carts images and tables are send together with the manuscript.

Title and the number of the charts and tables are placed above them while the explanations, abbreviations and comments are placed below. Images title and number is placed below and the image should include proper explanation.

**Discussion** section emphasize the key finding of the actual research and compares these result to other relevant literature data.

**Conclusion** section should not include more than 150 words and shoul be drown from the relevant elaborated results.

**Acknowledgment and Author contributions** sections are displayed after the conclusion and before the reference section.

### **REFERENCES**

This sections include only the cited references. **The references** are listed in order of appearance in the paper and the citation is standard numbers enclosed in small brackets in the same line with the text ( ).

For each reference if more than three authors appear provide the names of the first three authors and followed by **et al.**

#### **Examples:**

Journal references:

Nirmala BC, Kumari G. Foot drop after spinal anaesthesia: a rare complication. Indian J Anaesth. 2011; 55: 78 – 79.

Lynch EP, Lazor MA, Gellius JE, et al. The Impact of Posoperative Pain on the Development of Postoperative Delirium. Anesth Analg 1998; 86:781-785.

#### **2. Journal supplements:**

AzmanJ, Frkovic V, Bilic L, et al. Korelacija I regresija. Acta Med Croat 2006;60 (suppl I):81-89. | 70 |

### 3. Books

Brown, D.L. Spinal, epidural, and caudal anesthesia. In R.D. Miller Miller's Anesthesia, 6th edition. Philadelphia: Elsevier Churchill Livingstone; 2005.p 98-198

### 4. Doctoral or master thesis

Jelisavac Cosic S. Urokinazni I tkivni aktivator plazminogena i njihov inhibitor u raku dojke (Master thesis). Zagreb: Farmaceutsko-biohemijski fakultet 2004, p.50

### 5. Electronic reference

Dag Stat. Mackinnon A. Available from: <http://www.mhri.cdu.au/biostats>. Accessed May 5th 2006.

Webster NR. The anaesthetist as peri-operative physician. Anaesthesia. <http://dx.doi.org/10.1046/j.1365-2044.2000.01722.x>

References used from abstracts are marked as **(abstr)**., and from letters with **(letter)**

## ***MANUSCRIPT SUBMISSION***

Prepared manuscript should be submitted electronically to:

**macedoniananesthesiology@gmail.com.**

**All manuscripts that don't fulfill the above criteria will not be accepted for reviewing**

## ***Accompany letter ANNEX no. 1***

I \_\_\_\_\_ . Here by declare that the article \_\_\_\_\_ (NAME OF THE ARTICLE) has not been previously published (fully or partialy) previously.

We autors \_\_\_\_\_ (FULL NAME AND SURNAMES OF THE AUTORS AND SIGNATURES) are responsible for the etic, profesional and scientific content of the study.

I \_\_\_\_\_ (THE FIRST AUTHOR FULL NAME) declare Conflict of interest or declare non Conflict of interest.

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Скупи 3 бр.55, 1000 Скопје, Р.Македонија  
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