Seasonality of common cardiorespiratory risk factors and pulmonary effects of dopamine in cardiac surgery patients

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I. Background

I.1. Study I.

I.1.1. Public health characteristics

Cardiovascular diseases are a leading cause of death worldwide, accounting for a significant portion of global mortality. They are responsible for about one-third of all deaths, resulting in 18 million deaths in 2019. The main risk factors for cardiovascular diseases include unhealthy diets, smoking, and physical inactivity leading to obesity and diabetes. The risk of developing diabetes increases with age, and consequently, the number of cardiovascular diseases as macrovascular complications of diabetes, as well as related deaths, also rises.

I.1.1.1. Diabetes mellitus

I.1.1.1.1. Type 2 diabetes mellitus: epidemiology

The prevalence and incidence of type 2 diabetes mellitus (T2DM) are rising among the adult and elderly populations worldwide. In 2021, diabetes mellitus affected 10.5% of the global population, which translates to 537 million people, and this number is expected to increase by 2045. In Hungary, every eleventh person suffered from diabetes in 2020, and while the prevalence is slightly decreasing, the incidence is showing an upward trend. This is mainly due to the ageing population and the demographic pattern of an ageing society. The increasing number of people with diabetes places a growing burden on the healthcare system. Consequently, the rise in cardiovascular diseases leads to more cardiac surgical interventions.

I.1.1.1.2. Type 2 diabetes mellitus: pathophysiology

The most common form of diabetes is T2DM, which accounts for nearly 95% of all diabetes cases. T2DM is a chronic, complex, heterogeneous metabolic disease that is often asymptomatic in its initial stages and thus frequently diagnosed late, but its treatment lasts a lifetime. The first step in its pathophysiological background is insulin resistance, during which the effectiveness of secreted insulin decreases, and the body can no longer maintain a normoglycemic state. As a result of elevated blood glucose levels, glucose homeostasis is impaired, leading to relative insulin deficiency, which eventually results in absolute insulin deficiency. The disrupted metabolic milieu damages lipid metabolism, adversely affecting the vascular endothelium, resulting in functional and structural damage. Consequently, hemostasis shifts towards a thrombotic state. With endothelial damage, pathological autoregulatory mechanisms prevail, basal vascular tone increases, and an enhanced vasoconstrictive state occurs, which can lead to reduced tissue perfusion.

I.1.1.2. Smoking

I.1.1.2.1. Smoking: epidemiology

Similar to the increasing prevalence of diabetes mellitus, the number of smokers is also showing a rising trend. According to WHO estimates, by 2050, there will be nearly one and a half billion smokers worldwide. Among patients suffering from cardiovascular diseases, smoking is considered the primary cause of death in 10% of cases, including passive smoking. According to a survey by the Hungarian Central Statistical Office, in 2014, more than one in four adults in Hungary smoked daily, which was the third highest rate among the member states of the European Union.

I.1.1.2.2. Smoking: pathophysiology

Smoking increases the risk of sudden cardiac death, acute myocardial infarction, stroke, and coronary artery disease in both men and women. Smoking induces local inflammation of the endothelium and enhances the oxidative modification of low-density lipoprotein, thereby increasing the risk of atherosclerosis. The inflammation of the endothelium and the formation of peripheral plaques damage the endothelial structure, reducing the production and exogenous utilization of nitric oxide, which impairs the vasodilation capability of the blood vessels. As a result, due to the increased platelet aggregation ability and elevated levels of fibrinogen and tissue factor, hemostasis shifts towards a thrombotic state.

I.1.1.3. Ageing

I.1.1.3.1. Ageing: epidemiology

In the member states of the European Union, the life expectancy at birth for both men and women is increasing, with projections indicating an increase of almost 6 years for women and 4 years for men by 2050 compared to 2004 data. Globally, 9.3% of the population was elderly according to 2020 data. Hungary's situation is unique compared to the global situation, as low fertility rates are typically accompanied by worse mortality conditions. This resulted in a rapid increase in the proportion of the elderly population from 15.1% to 20.4% between 2000 and 2020, thus Hungary continues to be classified as an ageing society.

I.1.1.3.2. Ageing: pathophysiology

In advanced age, increased oxidative stress, inflammation, accelerated apoptosis, and a shift towards thrombosis are predominantly observed. Consequently, myocardial hypertrophy and valve defects can develop, and the risk of ischemic heart disease, heart failure, and arrhythmias, such as atrial fibrillation increases. Due to the more rigid structure of the blood vessel walls, systolic and pulse pressures rise, leading to poorer adaptation to environmental changes.

I.1.2. Seasonal variations

According to scholarly publications, it is well known that the occurrence of severe cardiovascular diseases is more frequent in winter and follows a seasonal pattern. In addition to environmental factors, other pathophysiological factors are also responsible for the worsening of cardiovascular diseases, such as increased catecholamine levels due to sympathetic nervous system activation, elevated serum cholesterol levels, a prothrombotic shift, increased fibrinogen levels, and vitamin D deficiency. Consequently, in patients with T2DM, a seasonal exacerbation of clinical signs and symptoms is expected, which may necessitate modifications to treatment strategies, including the need for cardiac surgeries.

I.2. Study II.

I.2.1. Cardiopulmonary bypass

In cardiac surgeries requiring extracorporeal circulatory support, cardiopulmonary bypass (CPB) is frequently used. The primary goal during CPB is to preserve the perfusion of extracardiac organs. The use of CPB allows for the maintenance of perfusion, increased anoxia tolerance of the heart, cardiac arrest, and the opening of the heart chambers and the ascending aorta. This method significantly impacts thermoregulation, fluid balance, hemostasis, and the inflammatory response.

I.2.2. Pathophysiological aspects of CPB

The cardiac surgery using CPB initiates a wide spectrum of pathophysiological changes, including harmful respiratory system alterations, and deterioration of post-separation cardiac pump function. Cardioplegia, as well as cardiac surgical techniques, can impair the pump function of the heart, often necessitating the administration of positive inotropes, such as dopamine, due to the deterioration of post-cardiotomy pump function. Additionally, during CPB, the lungs are excluded from their physiological pulmonary system (the bronchial system remains intact), leading to potential lung ischemic and reperfusion damage, along with the formation of atelectatic lung areas due to heterogeneous ventilation.

I.2.3. Application of dopamine after CPB

Due to impaired cardiac pump function, dopamine is generally administered as a positive inotropic agent in low to moderate doses (2-5 μg/kg/min), utilizing its effect to increase cardiac output. Dopamine's effect on β-receptors reduces bronchial smooth muscle tone, thereby decreasing airway resistance, and also impacts the viscoelastic properties of airway tissues. Literature reports differ in their views on the effect of dopamine on gas exchange; in many cases, while dopamine improves respiratory mechanics, it has been observed to impair gas exchange.

II. Aims and hypotheses

II.1. Study I.

In the first study of this dissertation, our hypothesis was that since diabetes mellitus is known to increase the incidence of cardiovascular diseases, and smoking, obesity, and old age also affect the state of the vascular system, the increasing number of cardiac surgical interventions might show seasonal variations.

Our research aim was to investigate the seasonal fluctuations in the relative incidence of cardiac surgeries performed within a 12-year period in relation to diabetes mellitus, as well as other factors affecting the state of the vascular system such as smoking, obesity, and advanced age. Additionally, we sought to examine the potential seasonal variations in cardiovascular risk factors (blood pressure, serum triglycerides, cholesterol, and glucose levels) as a secondary objective.

II.2. Study II.

In the second study of this dissertation, we aimed to clarify the effects of dopamine on the respiratory system, respiratory mechanics, and gas exchange in patients undergoing cardiac surgery with CPB.

III. Methods

III.1. Study I.

III.1.1. Ethics approval

The ethical approval for the study (274/2018/a) was granted by the Human Research Ethics Committee of the University of Szeged (Chair, Prof. T. Wittmann) on January 21, 2019. (NCT03967639).

III.1.2. Study design and population

At our institution (Cardiac Surgery Unit, Second Department of Internal Medicine and Cardiology Center at the University Hospitals of Szeged, Hungary), we conducted a retrospective, consecutive study between January 1, 2007, and December 31, 2018, analyzing data from 9,838 consecutive adult patients. According to our clinical practice, in the absence of a waiting list, interventions were performed within 5 days based on the severity of the condition after its assessment. This allowed us to analyze the true frequency of procedures without waiting list delays.

Cardiac surgery patients were categorized based on medical records into the following groups or combinations of groups. In accordance with the diagnostic criteria of the American Diabetes Association (ADA), patients were classified into the diabetes group if their medical history included T2DM and/or hemoglobin A1c > 6.5% . For identifying smokers, we used the criteria from the National Health Statistics Center; individuals were classified as smokers if they currently smoked (had smoked at least 100 cigarettes in their lifetime and were currently smoking), daily smokers (had smoked at least 100 cigarettes in their lifetime and currently smoked every day), or former smokers (had quit smoking <12 months ago).

We considered patients to be elderly if they were older than the average life expectancy published by the Hungarian Central Statistical Office for Southern Hungary during the study period (≥72 years for men and ≥79 years for women). Obesity was assessed according to the World Health Organization definition as a body mass index (BMI) ≥30 kg/m². Upon admission, non-invasive systolic and diastolic blood pressure values were recorded, while serum triglyceride, cholesterol, and glucose levels were measured from venous blood samples taken during the initial blood tests after hospital arrival. Criteria for exclusion from the study included type 1 diabetes, chronic respiratory diseases, and conditions involving unstable circulation (e.g., acute bleeding or signs of cardiac tamponade).

III.1.3. Monthly average temperature data

Average monthly temperature data for the study period were obtained from the database of the Hungarian Meteorological Service.

III.1.4. Data processing and statistical analyses

Statistically significant differences between the study groups for continuous variables were assessed using one-way analysis of variance (ANOVA), followed by Bonferroni post-hoc tests. Pearson's chi-square test was used to evaluate differences between categorical variables. The monthly proportion of surgeries related to different diseases was calculated based on the number of new cardiac surgeries performed on patients with the specific risk factor (individually and in combination; e.g., only T2DM; T2DM and smoking; T2DM, smoking, and elderly), and then divided by the total number of cardiac surgeries performed in the same month.

To determine the seasonality of monthly proportions of surgeries related to blood pressure, triglyceride, cholesterol, and glucose levels during the study period, we used Walter–Elwood and negative binomial regression methods, assuming that the data follow a sinusoidal curve. Walter and Elwood described the calculation of the goodness of fit for their methods, which we also took into account. Diabetes, ageing, smoking, obesity, and gender were considered as potential risk factors for cardiac surgeries. To quantify the quality of seasonality, we calculated the relative change (peak-to-mean)/mean and compared seasonal amplitudes. Statistical analyses were performed using Stata software package (version 17, Statacorp, College Station, Texas), with p-values less than 0.05 considered statistically significant. The diagrams were prepared using SigmaPlot software (Version 13, Systat Software, Inc., Chicago, IL, USA).

III.2. Study II.

III.2.1. Ethics Approval

The prospective, non-randomized clinical trial was approved by the Human Research Ethics Committee of the University of Szeged (WHO 2788). After receiving comprehensive information about the study, patients provided their written consent to participate. The study was registered on the ClinicalTrials.gov website (NCT04753008).

III.2.2. Patients

We prospectively and consecutively examined patients who underwent elective open-heart surgery. The study included 157 patients (99 men and 58 women), with an average age of 64 years (ranging from 32 to 79 years).

III.2.3. Anesthesia and Surgery

One hour before the surgery, all patients were premedicated with intramuscular morphine (0.07 mg/kg) and midazolam (0.07 mg/kg). Anesthesia induction was achieved with intravenous midazolam (30 µg/kg), sufentanil (0.4-0.5 µg/kg), and propofol (0.3-0.5 mg/kg). Anesthesia maintenance was provided with an intravenous propofol infusion (50 µg/kg/min). For muscle relaxation, an intravenous bolus of rocuronium was administered (0.6 mg/kg for induction and 0.2 mg/kg every 30 minutes for maintenance) to ensure neuromuscular blockade. Following induction, endotracheal intubation was performed (ID: 7, 8, or 9 mm), and volume-controlled ventilation mode was used (frequency: 10-14/min, tidal volume 7 ml/kg, PEEP: 4 cm H_2O, FiO2 initially 0.5, increasing to 0.8 after CPB) with a ventilator (Dräger Zeus, Lübeck, Germany). Prior to CPB, the membrane oxygenator was primed with 1500 ml of lactated Ringer's solution. Efforts were made to achieve adequate anticoagulation (activated coagulation time >400 seconds) using heparin at a dose of 300 U/kg. Mild hypothermia (i.e., esophageal temperature of 32°C) was routinely induced. During CPB, mechanical ventilation was stopped, and the ventilator was disconnected without applying positive airway pressure. Before restarting ventilation, the lungs were inflated three times to achieve a peak pressure of 30 cm H_2O, and then maintained at this pressure for three seconds.

III.2.4. Characterization of gas exchange

To characterize gas exchange, arterial and central venous blood samples were taken at each protocol stage. We measured the partial pressures of oxygen and carbon dioxide in the arterial blood (PaO_2 and $PaCO_2$) and venous blood (PvO_2 and $PvCO_2$) using a Radiometer ABL™ 505 (Copenhagen, Denmark), as well as the arterial (SaO_2) and venous (SvO_2) oxygen saturations. The lung oxygenation index, or Horowitz index, was determined as the PaO_2/FiO_2 ratio.

The intrapulmonary shunt fraction (Qs/Qt) was calculated using the Berggren equation:

$$\frac{Qs}{Qt} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

where CcO_2, CaO_2, and CvO_2 represent the oxygen content of pulmonary capillary, arterial, and central venous blood, respectively.

To determine CcO_2, the following equation was used, assuming 100% hemoglobin O_2 saturation in the pulmonary capillaries:

$$CcO_2 = 1{,}34xHb + 0{,}0031xPAO_2$$

where 1.34 ml/g is the Hüfner constant, Hb is the hemoglobin concentration in grams, the total dry gas pressure is 713 mmHg, and the respiratory exchange ratio is 0.8.

The partial pressure of alveolar oxygen (PAO_2) was derived from the alveolar gas equation:

$$PAO_2 = 713xFiO_2 - \frac{PaCO_2}{0{,}8}$$

III.2.5. Assessment of V/Q matching using time and volumetric capnography

During ventilation, a mainstream capnograph (Novametrix, Capnogard, Andover, MA) was incorporated into the ventilatory circuit. A pneumotachograph (Piston Ltd., Budapest, Hungary) was used to record central airflow. The phase-3 slope of the time (Sn3T) and volume (Sn3V) capnograms was determined by fitting a linear regression line to the last 60% of phase 3. From the volume capnograms, we also calculated the dead space fraction. The physiological dead space according to Bohr (VDB) refers to the alveolar volume that has ventilation but reduced perfusion.

$$\frac{VDB}{VT} = \frac{(PACO_2 - PECO_2)}{PACO_2}$$

where $PACO_2$ is the average partial pressure of CO_2 in the alveoli measured at the midpoint of phase 3 of the capnogram, and $PECO_2$ is the partial pressure of CO_2 in the mixed expired air.

The Enghoff dead space (VDE) provides additional information about V/Q mismatch, as it includes not only VDB but also those alveolar regions with maintained perfusion but reduced ventilation (intrapulmonary shunt). VDE was calculated as follows:

$$\frac{VDE}{VT} = \frac{(PaCO_2 - PECO_2)}{PaCO_2}$$

III.2.6. Measurement of airway and lung tissue mechanics by forced oscillations

To measure changes induced by dopamine in the mechanical properties of the airways and lung tissues, we used the low-frequency forced oscillation technique. In this method, a speaker was placed inside a closed box, which served as the signal generator. We integrated two flexible tubing sections into the respiratory circuits, allowing us to selectively measure and ventilate. The returning signal from the airways was detected as input pressure and flow using a pneumotachograph, from which the input impedance (ZL) signal was recorded. Using mathematical methods, we calculated the mechanical parameters of the airway tissues (R = total airway resistance, Raw = resistance of oscillating airways during forced oscillation, G = tissue damping, H = tissue elasticity, C = compliance, Iaw = tissue inertance).

III.2.7. Measurement protocol

We recorded our measurements at three time points: first, 5 minutes after median sternotomy and stabilization of the condition, just before the initiation of CPB (pre-CPB); second, 5 minutes after the termination of CPB (post-CPB); and third, 5 minutes after the initiation of dopamine infusion (INT). For the control group, measurements were taken at the same time intervals without the administration of inotropic agents.

III.2.8. Statistical Analyses

The variability in the measured variables was expressed within the 95% confidence interval of the mean. The normality of the data was assessed using the Kolmogorov-Smirnov test with Lilliefors correction. A two-way repeated measures analysis of variance was applied to all measured variables. For comparisons between the study groups at different stages of the protocol, the Holm-Sidak multiple comparison procedure was used. Differences in demographic, anthropometric, and clinical characteristics were evaluated using the chi-square test. Statistical tests were performed using SigmaPlot software (Version 14, Systat Software, Inc., Chicago, IL). All p-values were two-sided.

IV. Results

IV.1. Study I.

IV.1.1. Patient population

Out of 9,881 individuals, 27 patients were excluded from our study due to incomplete anthropometric data, blood pressure readings, or blood sample analyses. Type 1 diabetes was diagnosed in 16 patients, and since the phenotype of type 1 diabetes differs fundamentally from that of type 2 diabetes mellitus, these individuals were also excluded. Ultimately, data from 9,838 adult patients were analyzed.

IV.1.2. Anthropometric data and clinical characteristics

The proportion of patients with T2DM was 38.4%, which is consistent with the literature indicating that 30-40% of patients undergoing heart surgery suffer from diabetes mellitus. The observed male predominance (63.1%) in the entire study population was also present in all subgroups, except for the patients with only T2DM (51.4%).

Patients with T2DM had significantly higher body weight (84.4 vs. 77.6 kg, $p<0.001$) and BMI (31.0 vs. 28.1 kg/m², $p<0.001$), while smoking was associated with a lower BMI (27.1 kg/m²; $p<0.001$). Compared to patients without risk factors, aortic diseases were more common in older patients ($p<0.05$), while the prevalence of adult congenital heart diseases was lower in those with T2DM, smokers, and older patients ($p<0.05$). The proportion of coronary artery disease was generally higher among patients with T2DM and smokers ($p<0.05$).

IV.1.3. Seasonal variabilities: significant risk factors

No statistically significant seasonal variation was detected regarding sex ($p=0.81$) and BMI ($p=0.75$), nor in the cases of individual heart surgeries ($p = 0.30$ for aortic stenosis, $p = 0.58$ for mitral insufficiency, $p = 0.51$ for coronary artery disease, and $p = 0.75$ for coronary artery disease with mitral insufficiency).

Significant seasonal variations were observed for T2DM ($p<0.02$), smoking ($p<0.001$), and old age ($p<0.001$). Therefore, we also examined these factors individually, as well as their pairwise combinations. For the relative incidence of heart surgeries, patients with only diabetes (9.6%, $p<0.02$) and those who were only smokers (16.4%, $p<0.001$) exhibited seasonal fluctuations with a winter peak and a summer trough. Conversely, among patients who were only elderly

(20.3%, $p<0.001$), more heart surgeries were observed in the summer, indicating a different seasonal variation.

The combined presence of diabetes and smoking had an additive effect on seasonality, with the peak of heart surgeries also occurring in the winter, and the highest seasonal variability was observed in this patient group (107%, $p<0.001$). When an age-related factor with different seasonal patterns was associated, no significant difference was observed; for elderly patients with T2DM ($p = 0.66$) or elderly smokers ($p = 0.46$), the seasonal variation was lost, although these patients still had an increased risk that needed to be accounted for.

IV.1.4. Risk factors for cardiovascular complications

Regarding potential cardiovascular risk factors, we examined systolic and diastolic arterial blood pressure, as well as serum triglyceride, total cholesterol, and glucose levels in patient groups where these risk factors might cause significant seasonal changes. Significant seasonal variation was observed in patients with T2DM for systolic blood pressure ([peak-trough]/trough: 6.1%, $p<0.001$, peak in February-March), diastolic blood pressure (4.4%, $p<0.05$, peak in January), and serum triglyceride levels (17.1%, $p<0.005$, peak in December). Additional significant seasonal variation was observed in smokers for systolic and diastolic blood pressure (6.1% and 6.5%, $p<0.001$ for both, peaking in February), as well as in elderly patients for cholesterol levels (9.1%, $p<0.001$, peak in February).

IV.2. Study II.

IV.2.1. Patient population

Patients were classified into a dopamine group (DA, n=52) and a control group (control, n=105) based on their need for positive inotropic support due to reduced cardiac pump function. A multimodal approach was used to determine dopamine requirements. Exclusion criteria for our study included age over 80 years, chronic respiratory disease, and the need for high-dose medication or mechanical circulatory support.

IV.2.2. Anthropometric data and group allocations

In terms of sex, age, height, weight, and types of surgery, the protocol groups did not differ significantly from each other.

IV.2.3. Lung mechanical parameters

In the context of CPB, mechanical parameters showed increased values, with higher values in Raw and G, and smaller, but significant changes in H, R, and C ($p<0.001$ for all). The effect of dopamine led to a significant decrease in Raw, G, and H ($p<0.001$ for each), whereas the values in the control group remained unchanged.

IV.2.4. Capnogram shape factor and dead space parameters

The normalized phase 3 slope of both time and volumetric capnograms increased after CPB in both groups. The VDB decreased in both groups ($p<0.001$ for both), while the VDE increased significantly only in the DA patient group ($p<0.005$). In the DA group, Sn3T, Sn3V, and VDE decreased significantly ($p<0.01$ for all), but no significant change was observed in VDB.

IV.2.5. Gas exchange and intrapulmonary shunt

CPB significantly reduced the PaO_2/FiO_2 ratio, increased the Qs/Qt ratio, and decreased both SvO_2 and the $PvCO_2$-$PaCO_2$ difference in both groups ($p<0.001$ for all). In the DA group, there were no significant changes in PaO_2/FiO_2 and Qs/Qt values, but a significant increase in SvO_2 and a significant decrease in $PvCO_2$-$PaCO_2$ were observed ($p<0.001$ for both).

V. Discussion

V.1. Study I.

In our study, covering a 12-year period, we observed that in non-elderly patients with diabetes and/or smokers, there were more cardiac surgeries in the winter, whereas in elderly patients who were neither diabetic nor smokers, there were more surgeries in the summer. Factors with similar seasonal fluctuations, such as smoking and diabetes, had an additive effect on each other. However, when examining the combination of factors with different seasonal patterns, if elderly age was associated with smoking or diabetes, the seasonal differences counteracted each other, leading to the loss of seasonal variation.

V.1.1. Methodological considerations

The risk factors examined in terms of seasonal variations (diabetes, smoking, and old age) were defined based on objective, internationally well-established diagnostic criteria. Data recording throughout the study period was carried out by clinicians on the day before the surgery, including five anesthesiologists.

V.1.2. Seasonality of exacerbation of cardiovascular diseases in patients with T2DM

As observed in the study, the proportion of heart surgeries related to diabetes significantly increased during the coldest months of the year, and the systolic and diastolic blood pressure values, as well as serum triglyceride levels, followed the seasonal trend seen in the procedures. In diabetic patients, hyperglycemia and dyslipidemia disrupt the metabolic milieu, leading to endothelial dysfunction, which raises inflammatory, prothrombotic, and proliferative factors. Diabetic patients already have an increased vasoconstrictive state, which can worsen during the cold period, increasing the workload on the heart and exacerbating functional valve diseases.

V.1.3. Seasonality of exacerbation of cardiovascular diseases in smoking patients

In our population, the proportion of smokers undergoing heart surgery, without T2DM or advanced age, was lower compared to those with only T2DM, but showed a similar seasonal fluctuation with a winter peak and summer trough. In smokers, endothelial dysfunction leads to decreased release and bioavailability of NO. Consequently, the increased vascular tone and impaired vasodilatory capacity may be responsible for the seasonal variations observed in heart surgeries among smokers.

V.1.4. Seasonality of exacerbation of cardiovascular diseases in elderly patients

In contrast to smokers and T2DM patients, the proportion of elderly patients undergoing heart surgery peaked in the summer. This opposing morbidity trend can be attributed to the decreased elasticity of large conducting arteries. The reduction in arterial elasticity in elderly individuals acts as a predisposing factor for hypovolemia and hypotension. Accordingly, the significantly lower diastolic blood pressure observed during the summer months indicates that cardiovascular symptoms are likely to worsen during warmer periods.

V.1.5. Effects of combined cardiovascular risk factors

Seasonal variability disappeared when ageing was associated with diabetes or smoking. The absence of seasonality in these conditions can be attributed to the overlap of two sinusoidal waves with opposing phases but similar periodicities, resulting in the cancellation of the periodicity. However, it should be noted that these patients remain exposed to the individual risk factors of ageing, diabetes, or smoking.

V.1.6. Effects of other factors on epidemiology

There was no seasonal variation observed in relation to specific heart diseases (aortic stenosis, mitral valve insufficiency, or coronary artery disease). Consequently, seasonality is more likely related to the sensitivity of the peripheral vascular system to temperature changes rather than to the type of heart disease. This suggests that diabetes, smoking, and ageing are the primary seasonal-dependent factors, irrespective of the nature of the cardiac pathology.

V.1.7. Seasonal temperature pattern

Hungary is located in a temperate climate zone, characterized by four distinct seasons. According to the Meteorological Service, the monthly average temperatures were calculated from daily averages and served as the basis for our measurements. Given that a significant portion of the global population lives in similar climatic zones, our results are also significant in that they can be extended to a large part of the world's population.

V.2. Study II.

In a large cohort of patients who underwent heart surgery with CPB, we observed that dopamine's ability to improve the mechanics of the airways and lung tissues was associated with its benefits on V/Q matching. We demonstrated with forced oscillation measurements that dopamine can reverse the adverse changes in lung function caused by CPB. Additionally, capnography and blood gas analyses showed that these mechanical changes were associated with improved V/Q matching and ventilation of dead space, without any harmful consequences for oxygenation or intrapulmonary shunt.

V.2.1. Effects of CPB

The effects of CPB include both local and systemic inflammatory responses, with one of the most commonly affected organs being the lungs, leading to multiple organ failure. As a result, the airway mucosa thickens, local and extensive bronchoconstriction occurs, and due to interstitial fluid retention, there is a deterioration in the viscoelasticity of the airways and lung tissues. This leads to a heterogeneous decrease in the ventilated lung volume and the formation of atelectatic lung regions. The deterioration in the dissipative and elastic parameters of the lung parenchyma caused by CPB is primarily attributed to heterogeneous alveolar ventilation. The decrease in VDB observed with CPB is attributed to increased bronchial tone and local bronchoconstriction caused by hypocapnia, while the increase in VDE is considered a consequence of persistent atelectasis. Additionally, due to hemodilution anemia, decreased cardiac output, and reduced arterial oxygen content, we observed a decrease in SvO_2 values.

V.2.2. Effects of dopamine

The damage to airway and tissue mechanics caused by CPB significantly improved with intravenous dopamine infusion. This improvement can be attributed to a reduction in interstitial alveolar edema and the opening of predominantly peripheral alveolar compartments that were most dominant within the 5-minute time window. The effect of dopamine was reflected in the decrease of the normalized Phase 3 slope, both in volume and time capnograms, indicating improved V/Q matching and homogenization of lung ventilation. Due to the improved lung mechanics and the concomitant increase in pulmonary perfusion, we did not observe any changes in VDB, but dopamine did reduce VDE. This suggests that dopamine influences the relative volume of low V/Q ratio alveoli, meaning that with an increase in cardiac output and CO_2 elimination, CO_2 production remains stable.

One of the most important findings of this study was that after CPB, the administration of dopamine did not change the Horowitz index or Qs/Qt, which can be explained by the fact that dopamine, by homogenizing lung ventilation, also improved pulmonary perfusion.

VI. Conclusions

VI.1. Study I.

In summary, our study confirmed that the relative incidence of cardiac surgical interventions shows seasonal fluctuations in patients with T2DM, as well as in elderly and smoking patients. These seasonal fluctuations align with those observed in blood pressure values. Our study also highlights that, contrary to international guidelines (ADA), which recommend annual check-ups, patients should undergo at least two annual assessments (one in the autumn-winter period and another in the spring-summer period). This approach, which includes monitoring blood pressure and lipid panels, represents a significant step towards personalized and individualized treatment strategies, as well as providing an opportunity to potentially avoid cardiac surgical interventions.

VI.2. Study II.

In summary, this study demonstrated that dopamine can alleviate airway function and ventilation heterogeneity induced by CPB. Although the beneficial effects of dopamine on pulmonary mechanics were not reflected in physiological dead space ventilation or intrapulmonary shunting, there was no evidence of adverse gas exchange abnormalities following weaning from CPB. Therefore, this inotropic agent can be safely recommended during the postoperative period after CPB to improve cardiac function and mitigate impaired lung function, without posing a risk of detrimental effects on V/Q matching. Furthermore, our results suggest that when using positive inotropes, recruitment maneuvers and/or increased ventilation may be necessary to prevent deterioration in gas exchange.

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Publications

Publications included in the present thesis

I. Peták F*, **Kovács BN***, Agócs S, Virág K, Nyári T, Molnár A, Südy R, Lengyel C, Babik B. Seasonal changes in proportion of cardiac surgeries associated with diabetes, smoking and elderly age. *PLoS One.* 22;17(9):e0274105, 2022. doi: 10.1371/journal.pone.0274105
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II. Peták F, Balogh ÁL, Hankovszky P, Fodor GH, Tolnai J, Südy R, **Kovács BN**, Molnár A, Babik B. Dopamine Reverses Lung Function Deterioration After Cardiopulmonary Bypass Without Affecting Gas Exchange. *J Cardiothorac Vasc Anesth.* 36(4):1047-1055, 2022. doi: 10.1053/j.jvca.2021.07.033.

Publications related to the present thesis

I. **Kovács BN**, Südy R, Peták F, Balogh ÁL, Fodor HG, Tolnai J, Korsós A, Schranc Á, Lengyel C, Babik B. Respiratory consequences of obesity and diabetes. *Orv Hetil.* 163(2):63-73, 2022. doi: 10.1556/650.2022.32335.