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

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Publications

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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.

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Table of contents

GLOSSARY OF TERMS

AAA	Aortic arch reconstruction
AD	Aortic dissection
ADA	American Diabetes Association
AI	Aortic insufficiency
AS	Aortic stenosis
AGEs	Advanced glycation end products
AVP	Aortic valve plasty
BMI	Body mass index
C	Compliance
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CaO_2	Oxygen content of the arterial blood
CcO_2	Oxygen content of the pulmonary capillary blood
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CvO_2	Oxygen content of the central venosus blood
DCM	Dilated cardiomyopathy
EI	Infective endocarditis
FiO_2	Fraction of inspired oxygen
G	Lung tissue damping
GUCH	Grown-up congenital heart disease
H	Lung tissue elastance
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
HCSO	Hungarian Central Statistical Office
Iaw	Airway inertance
LAM	Left atrial myxoma
LDL	Low-density lipoprotein
MI	Mitral insufficiency
MS	Mitral stenosis
NO	Nitric oxide
PaO_2	Partial pressure of oxygen in the arterial blood
PAO_2	Alveolar oxygen tension

$PaCO_2$	Partial pressure of carbon dioxide in the arterial blood
$PACO_2$	Partial pressure of carbon dioxide in the alveolus
PEEP	Positive end-expiratory pressure
Ptr	Tracheal pressure
PvO_2	Partial pressure of oxygen in the central venous blood
$PvCO_2$	Partial pressure of carbon dioxide in the central venous blood
Qs/Qt	Intrapulmonary shunt fraction
R	Total respiratory resistance
Raw	Airway resistance
ROS	Reactive oxygen species
SaO_2	Oxygen saturation in the arterial blood
SM	Smoking
$Sn3_T$	Normalized phase-3 slope of the time capnogram
$Sn3_V$	Normalized phase-3 slope of the volumetric capnogram
SvO_2	Oxygen saturation in the central venous blood
T2DM	Diabetes mellitus type 2
VDB	Ventilation dead space fraction according to Bohr
VDE	Ventilation dead space fraction according to Enghoff
VDF	Ventilation dead space fraction according to Fowler
VT	Tidal volume
WHO	World Health Organization
ZL	Input impedance of the lung

I. Background

I.1. Study I.

I.1.1. Public health characteristics

Cardiovascular diseases are the leading cause of mortality worldwide, responsible for approximately one-third of all deaths, resulting in a loss of 18 million lives in 2019 [1]. The most significant behavioral risk factors for cardiovascular diseases are smoking, unhealthy diet, and physical inactivity, which may contribute to obesity and diabetes [1]. Additionally, ageing increases the risk of developing diabetes and, consequently, cardiovascular morbidity and mortality [2]. Accordingly, these risk factors are the focus of the first study included in the present thesis.

I.1.1.1. Diabetes mellitus

I.1.1.1.1. Type 2 diabetes mellitus: epidemiology

The prevalence of type 2 diabetes (T2DM) shows a strong increase worldwide. In 2021, it affected 10.5% of the world's population (i.e., 537 million people) [3]. Both the prevalance and the absolute number of the diabetic patients are expected to rise markedly by 2045 [4, 5]. Moreover, about a third of people with diabetes are currently unaware of their condition, according to the IDF Diabetes Atlas [3]. In Hungary, approximately one in eleven adults suffered from diabetes in 2020. However, no exact up-to-date data exist on the frequency of diabetes due to the absence of a central national register. Although there has been a slight decrease in the incidence (i.e., number of new patients) in Hungary, the prevalence (i.e., the total number of patients with diabetes) is steadily increasing due to effective medications and the ageing population [6].

In countries with advanced healthcare systems, the number of complications associated with diabetes has decreased in recent decades. However, the human and financial resources devoted to diabetes remain substantial [7]. This phenomenon is also observed in Hungary, where the complex care of patients suffering from T2DM places an increasing burden on the healthcare system, and the number of hospital days for patients is rising [8]. As part of this complex care, treatment of cardiovascular comorbidities should also be considered, including heart surgeries in the most severe cases.

I.1.1.1.2. Type 2 diabetes mellitus: pathophysiology

The most common form of diabetes is T2DM, accounting for almost 95% of cases in adults [9]. T2DM is a chronic, complex disease with a wide spectrum of systemic adverse consequences resulting from the pathological metabolic milieu.

The first step in the pathogenesis of T2DM is insulin resistance, where there is a reduced efficacy of the secreted insulin. At this phase, the circulating insulin is not able to maintain normoglycemia [10]. As the disease progresses, a gradually elevated insulin level is required to maintain relatively normal glucose homeostasis. As the disease advances, the balance of insulin demand and supply is disturbed, glucose homeostasis is impaired, and hyperglycemia results. At this stage, there is a defect in the amount of insulin released from the pancreatic β-cells, leading to both relative and absolute insulin insufficiency.

Due to the resulting relative insulin deficiency and hyperglycemia, a pathological metabolic state occurs, which also affects lipid metabolism. This pathological metabolic milieu has detrimental effects on the vascular endothelium, leading to both functional and structural damage. Hyperglycemia in T2DM directly, and fatty acids present in high concentrations in the plasma indirectly, enhance prothrombotic processes while weakening anticoagulation mechanisms, thereby shifting hemostasis towards a thrombogenic state.

As a result of this and other pathologically activated molecular signaling pathways, reactive oxygen species (ROS) are generated, and their levels exceed the amount of antioxidants. Activated ROS, along with oxidative and osmotic stress, contribute to the abnormal migration and proliferation of smooth muscle cells. These factors play a significant role in vascular remodeling, alongside increased vascular endothelial growth factor due to phosphokinase-C activation and increased collagen due to overexpression of transforming growth factor beta. Advanced glycation endproducts (AGEs) are formed by a non-enzymatic reaction between the amino groups of proteins and reducing carbohydrates [11]. The glycation cross-links that form in collagen molecules lead to structural and functional changes, contributing to a stiffer endothelial structure in patients with diabetes and damage to extracellular matrix proteins. This more rigid structure results in increased generalized vasoconstriction, raising the basal tone of blood vessels and increasing the likelihood of developing micro- and macrovascular complications of diabetes.

Furthermore, the vasoconstriction occurring in an already vasoconstrictive state leads to a greater decrease in local blood flow, resulting in incomplete tissue perfusion [12]. Thus,

endothelial damage and remodeling not only increase vasoconstriction but also impair other autoregulation and circulation redistribution abilities in patients with diabetes.

In diabetes, molecular and cellular changes lead to the inflammatory phenotype of endothelial cells exposed to chronic high serum glucose levels. This inflammatory phenotype results in increased apoptosis, expansion of the extracellular matrix, elevated permeability, increased vascular constrictor tone, and a prothrombotic shift in hemostatic balance [12,13,14,15,16,17,18].

I.1.1.2. Smoking

I.1.1.2.1. Smoking: epidemiology

Similar to the increasing prevalence of diabetes mellitus, there is a growing trend in the number of smokers. According to WHO estimates, there will be one and a half billion smokers worldwide by 2050 [19]. Smoking is reported as an underlying cause of death in 10% of patients with cardiovascular diseases [20]. Epidemiological research conducted since the 1950s has identified smoking as one of the main causes of death globally. Due to the increasingly widespread smoking habit among the young population, smoking is responsible for millions of deaths yearly, a substantial portion of which are due to passive smoking [21]. Smoking results in a two- to four-fold increase in the risk of sudden death [22]. Furthermore, it is well-documented that almost 70% of patients with atherosclerosis obliterans smoke, evidencing the relationship between smoking and the increased risk of peripheral vascular diseases [23].

According to a survey conducted by the Hungarian Central Statistical Office, more than one in four adults in Hungary smoked cigarettes daily in 2014, which was the third highest rate among the member states of the European Union [24]. Smoking is among the main risk factors for the development of cardiovascular diseases, which are the leading cause of death in Hungary.

I.1.1.2.2. Smoking: pathophysiology

Smoking increases the risk of heart attack, coronary artery disease (CAD), stroke, and sudden death [25, 26, 27]. It increases susceptibility to atherosclerosis, more frequently leads to the development of intermittent claudication and aortic aneurysms (especially in the abdominal section), and reduces the thickness of the carotid intima [23, 28]. The earliest manifestation of atherosclerosis is impaired vasodilation, occurring in both active and passive smokers [25]. Nitric oxide (NO) is responsible for the vasodilation function controlled by the endothelium [29]. In smokers, the expression and activity of endothelial NO synthase are altered, resulting in less NO available in the endothelial cells of the umbilical vein and coronary arteries, leading

to impaired vasodilation [30, 31]. NO is not only a vasoregulatory molecule but also acts as a regulatory molecule in inflammation, leukocyte adhesion, platelet activation, and thrombotic processes [29]. Smoking increases the number of leukocytes measurable in peripheral blood by 20-25% [32] and enhances the inflammatory response by elevating the levels of C-reactive protein, interleukin-6, and tumor necrosis factor-alpha [33, 34, 35, 36]. It also enhances the oxidative modification of low-density lipoprotein (LDL), leading to significantly higher levels of autoantibodies against oxidized LDL in smokers [37]. As a result, serum triglycerides, cholesterol, and LDL levels are higher in smokers [38].

Smoking reduces the availability of NO released from platelets and decreases sensitivity to exogenous NO, leading to increased platelet activation and adhesion [39, 40]. Consequently, platelets exhibit enhanced aggregation capacity, and thrombotic tendency increases [41, 42]. Additionally, smokers have elevated levels of fibrinogen and tissue factor [43, 44], and reduced levels of tissue plasminogen activator [45].

I.1.1.3. Ageing

I.1.1.3.1. Ageing: epidemiology

In the member states of the European Union (EU), life expectancy at birth for men and women is expected to grow. Compared to 2004 data (men: 75.3 years; women: 81.8 years), these numbers are projected to increase to 81.8 years for men and 86.9 years for women by 2050 [46]. The main reasons for this growth are multifactorial, related to health-conscious lifestyles, improved nutrition and food safety, developing public health and medical technologies, and reinforced public education. In 2020, the proportion of elderly people was 9.3% globally, a significant increase from 6.9% in the 2000s [47]. Forecasts suggest that the proportion of elderly may reach 15.9% by 2050 and 22.4% by 2100 [47].

Globally, in developed countries and regions with rapidly declining fertility, the proportion of elderly people is expected to be much higher. Japan had the world's oldest population in 2020, with 28.4% elderly. Hungary's situation is unique compared to the global context because low fertility is typically associated with worse mortality conditions. This resulted in a rapid increase in the proportion of elderly from 15.1% to 20.4% between 2000 and 2020 [46]. Accordingly, Hungary continues to be classified as an ageing country, characterized by an urn-shaped age pyramid [46].

Population ageing poses a major challenge for the healthcare system. Medical conditions such as diabetes and obesity become more frequent, and their progression accelerates with advancing age. The incidence of cardiovascular diseases also increases with age, from nearly 40% between 40-59 years, to 75% between 60-79 years, and 86% over the age of 80 [48, 49]. The most frequent manifestations of cardiovascular diseases in the elderly are hypertension, CAD, rhythm disorders (especially supraventricular tachyarrhythmias), congestive heart failure, and valvular diseases. Subsequently, cardiovascular diseases are responsible for the majority of deaths in individuals over 65 (82% of total deaths) [50].

The relationship between elderly age and diabetes has also been established [51]. The prevalence of T2DM increases with age [52].

I.1.1.3.2. Ageing: pathophysiology

The pathophysiological background of ageing includes a wide spectrum of molecular, cellular, tissue, and organ-level processes. Increased oxidative stress, inflammation, accelerated apoptosis, and thrombotic imbalance result in a decreased number of myocytes with hypertrophy. Additionally, calcification and fibrosis of the valves increase, and dysfunction of the sinoatrial node cells develops with age. These cellular-level pathologies can lead to myocardial hypertrophy, valve defects, and an increased risk of ischemic heart disease, heart failure, and rhythm disturbances such as atrial fibrillation [49, 50]. Furthermore, blood vessels are also targets of the ageing process, resulting in more rigid arterial walls, which contribute to elevated systolic and pulse pressures [53, 54].

In the absence of cardiovascular morbidity, these pathomechanisms can manifest as "frailty", which is considered a decreased ability to respond to external stress insults [55]. Frailty in elderly individuals represents an intermediate condition between healthy ageing and morbidity related to ageing.

I.1.2. Seasonal variations

It is well established that the incidence of severe cardiovascular diseases exhibits a seasonal pattern, with more frequent occurrences during winter [56, 57, 58, 59, 60, 61]. Environmental factors, such as air pollution [62], and several pathophysiological contributors may be responsible for these seasonal variations in the exacerbation of cardiovascular diseases. These factors include activation of the sympathetic nervous system and increased catecholamines [63], elevated serum cholesterol levels [64], prothrombotic shift in the hemostatic system via elevated fibrinogen levels [65, 66], decreased physical activity [56], and vitamin D deficiency

[67]. Moreover, the higher number of respiratory tract infections occurring in the winter correlates strongly with increased levels of fibrinogen, which is associated with proteins of the acute phase response, such as C-reactive protein, α1-antichymotrypsin, and neutrophil cell count [65].

Most of these pathological processes are influenced by diabetes [68]. Consequently, seasonal augmentation of clinical signs and symptoms can be anticipated in patients with T2DM, potentially requiring alterations in treatment strategy, including the need for cardiovascular surgery. Due to the seasonality of these factors, the number of cardiovascular diseases increases during the winter period, leading to a higher number of coronary artery bypass grafting (CABG) operations and/or heart surgeries for aortic dissection [69].

I.2. Study II.

I.2.1. Cardiopulmonary bypass

Cardiopulmonary bypass (CPB) is essential for open-heart surgeries, such as heart valve replacement or repair, and surgical correction of structural anomalies (e.g., septal defects, congenital heart diseases, aortic root diseases, and complications following myocardial infarction like left ventricular aneurysm or rupture of free ventricular walls). The use of CPB allows for the maintenance of whole-body perfusion, enabling the heart to be stopped and the heart chambers and/or ascending aorta to be opened.

This life support modality induces widespread and significant changes affecting hemostasis, heat regulation, fluid balance, inflammatory status, myocardial pump function, rhythm and conductance, and systemic blood flow patterns. Regarding the lungs during CPB with a left heart vent, pulmonary circulation is ceased while bronchial circulation is still maintained.

I.2.2. Pathophysiological aspects of CPB

Cardiac surgery with CPB initiates a broad spectrum of pathophysiologic changes, including deleterious effects on the respiratory system [70, 71, 72] and compromised cardiac pump function after weaning from CPB [73, 74].

The myocardial pump function may be impaired due to ceased coronary circulation resulting from the cross-clamping of the aorta, which is required to open the heart. Cardioplegia is applied to mitigate the effects of direct anoxia and/or ischemia. However, postcardiotomic pump failure often necessitates the administration of positive inotropes, such as dopamine, depending on the duration of myocardial ischemia and the effectiveness of myocardial

protection from ischemic injury [73, 74]. Furthermore, the deleterious consequences of CPB also manifest in the pulmonary system. The impairment is multifactorial, including the temporary cessation of pulmonary circulation leading to surfactant damage [71], a systemic inflammatory response affecting airway smooth muscle tone [75], and atelectasis due to the lack of alveolar ventilation during CPB. Additionally, the accumulation of extravascular fluid resulting from alterations in the alveolar-capillary membrane [76], a decrease in functional residual capacity [77], retention of airway secretions, and insufficient coughing due to pain may also contribute to lung dysfunction. These pathological processes compromise gas exchange and worsen respiratory mechanics [75, 78, 79, 80, 81].

I.2.3. Application of dopamine after CPB

The deleterious cardiac effects of CPB are often treated by administering positive inotropic agents, such as dopamine. Dopamine is commonly used in low-to-moderate doses (2-5 μg/kg/min) to increase cardiac output, and the dose-dependent circulatory effects of this inotrope are well-characterized [82,83]. In addition to its cardiovascular benefits, dopamine alters lung mechanics by diminishing bronchial smooth muscle tone, which decreases airway resistance [71, 84, 85, 86, 87, 88, 89, 90, 91], and affects respiratory tissue viscoelasticity [71, 90, 91]. However, this improvement in respiratory mechanics due to dopamine does not improve, and may even worsen, gas exchange. The decreased partial pressure of arterial oxygen (PaO_2) observed with dopamine use is explained by the increased cardiac output causing an elevated intrapulmonary shunt fraction [62, 63, 64, 65, 66].

The dissociated cardiopulmonary effects of dopamine may raise concerns among clinicians who observe improved lung mechanics but unchanged or somewhat worsened gas exchange [93, 94, 95, 96]. This seemingly controversial cardiopulmonary effect of dopamine has been demonstrated in healthy subjects [93, 95, 96] and in the presence of sepsis [94]. However, it remains unknown whether the beneficial effect on airway function or the potentially disadvantageous consequences on ventilation/perfusion (V/Q) matching of dopamine dominate the pathophysiologic and clinical aspects after weaning from CPB.

II. Aims and hypotheses

II.1. Study I.

The primary objective of the first study included in the present thesis was to determine whether the proportion of cardiac surgeries associated with diabetes requiring heart surgery exhibits seasonal variations, peaking during winter. To address this goal, we evaluated the monthly proportion of cardiac surgeries for patients with diabetes over a 12-year period at the cardiac surgery unit of a tertiary-care university hospital. As a secondary objective, we assessed whether factors affecting small blood vessels (smoking, ageing, and obesity) modulate the seasonal variability of T2DM, along with potential risk factors for cardiovascular complications (blood pressure, serum triglyceride, cholesterol, and glucose levels).

The rationale for the study is that worsening and/or exacerbation of cardiovascular complications necessitating surgery can often be prevented with appropriate medical treatments in patients with diabetes. Thus, exploring this cold-related seasonal phenomenon may elucidate the need for more frequent patient follow-ups to prevent progression with timely preventive measures.

II.2. Study II.

In the second study of the present thesis, we aimed to clarify the effects of dopamine on the respiratory system by comparing its potential to alter respiratory mechanics and ventilation-perfusion matching in a large cohort of patients who underwent cardiac surgery with CPB.

We hypothesize that dopamine could be a viable therapeutic option in conditions where both cardiac and pulmonary functions are compromised, without introducing additional risks to adversely affect V/Q matching.

III. Methods

III.1. Study I.

III.1.1. Ethical approval

Ethical approval for this study (No. 274/2018/a) was provided by the Human Research Ethics Committee of Szeged University, Hungary (Chairperson: Prof. T. Wittmann) on January 21, 2019. The study was registered at ClinicalTrials.gov (NCT03967639).

III.1.2. Study design and population

Medical records were retrospectively analyzed for all 9,838 consecutive adult patients who underwent surgery at our institution (Cardiac Surgery Unit, Second Department of Internal Medicine and Cardiology Center at the University Hospitals of Szeged, Hungary) from January 1, 2007, to December 31, 2018. These patients underwent the entire spectrum of cardiac surgeries. Our clinical practice avoided a waiting list; therefore, all operations were performed within five days of establishing the need for surgical intervention. Patient records were discarded in cases of emergency reoperations due to tamponade or acute bleeding, as these events are not related to the exacerbation of cardiovascular disorders. Accordingly, patients were included in the analyses only after primary or redo open-heart surgeries.

Cardiac surgery patients were assigned to the following groups, or combinations of groups, based on hospital medical records. Patients were defined as having T2DM if their medical history included a diagnosis of T2DM and/or hemoglobin A1c (HbA1c) > 6.5%, in accordance with the diagnostic criteria of the American Diabetes Association [68].

Since almost all (99.6%) patients with diabetes had T2DM, and the etiology and pathophysiological characteristics of type 1 diabetes mellitus differ from those of T2DM, only T2DM patients were included in the analyses, with an average of 8.6 years diagnosed disease period. Among T2DM patients, 25.8% were treated with insulin. T2DM patients treated with insulin or oral antidiabetics were pooled in the final analyses.

Patients were assigned to the smoking group based on the definitions of the National Center for Health Statistics [97]; current smokers (smoked 100 cigarettes in their lifetime and currently smoke cigarettes), everyday smokers (smoked at least 100 cigarettes in their lifetime and currently smoke every day), or ex-smokers (ceased tobacco use <12 months ago). Patients were considered elderly if they were older than the average life expectancy age in southern Hungary published by the Hungarian Central Statistical Office during the study period: ≥72 years for

males and ≥79 years for females [98]. Obesity was classified according to the definition of the World Health Organization as body mass index (BMI) ≥30 kg/m² [99]. Individual seasonal effects of these factors were analyzed on a monthly basis. To identify the coexistence of these factors with potential additive or regressive effects on seasonal changes, the combined occurrence of statistically significant factors was also examined.

Noninvasive systolic and diastolic blood pressure values were registered at admission, and serum triglyceride, cholesterol, and glucose levels were measured from venous blood samples collected from the first blood samples after arrival at the hospital.

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 by one-way analysis of variance followed by Bonferroni's post-hoc tests. Pearson's Chi-squared tests were used to evaluate differences in categorical variables. The monthly proportion of surgeries associated with different disorders was calculated as the number of new patients undergoing cardiac surgeries with a given risk factor (independently of the other two risk factors, alone, and in combination; e.g., T2DM alone; T2DM and smoking; T2DM, smoking, and elderly) divided by the total number of cardiac surgery patients in the same month.

The seasonality of the monthly aggregated proportion of surgeries associated with the observed disorders and values for blood pressure, triglyceride, cholesterol, and glucose during the study period was assessed using Walter–Elwood and negative binomial regression methods [100], assuming that the data followed a sinusoidal curve with a periodicity of one year. Geometric models were used to investigate seasonality by assuming that seasonal fluctuations of an event occur on a fixed date every year and can be described using cyclic patterns over time. The power of the Walter-Elwood test is 100% [101], and the percentage of change (variation) is the main effect size for the association between seasonal variation and health parameters. The deviance statistic was used to check the goodness of fit for negative binomial regression models. Similarly, Walter and Elwood also described a goodness of fit calculation for their methods [100], which was also taken into account.

Diabetes, ageing, smoking, obesity, and gender were considered possible risk factors for cardiac surgeries. Relative change (peak–mean)/mean was calculated to quantify the severity of seasonality and to compare seasonal amplitudes. Statistical analyses were performed using the Stata software package (version 17, StataCorp, College Station, Texas), and p-values < 0.05 were considered statistically significant. The charts were prepared using the SigmaPlot software package (version 13, Systat Software, Inc., Chicago, IL, USA).

III.2. Study II.

III.2.1. Ethical Approval

This single-center prospective non-randomized clinical trial was approved by the Human Research Ethics Committee of the University of Szeged, Hungary (No. WHO 2788). Written informed consent was obtained from the patients who participated in the study. The study was registered at clinicaltrials.gov (NCT04753008). All methods were carried out in accordance with the relevant guidelines and regulations, and this report includes every item in the CONSORT checklist for a prospective non-randomized clinical trial.

III.2.2. Patients

Patients who underwent elective open cardiac surgery were examined in a prospective and consecutive manner. This study included 157 patients (99 men and 58 women), with an average age of 64 years (range 32–79 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 was induced using intravenous midazolam (30 μg/kg), sufentanil (0.4-0.5 μg/kg), and propofol (0.3-0.5 mg/kg) and was maintained with an intravenous infusion of propofol (50 μg/kg/min). Intravenous boluses of rocuronium (0.6 mg/kg for induction and 0.2 mg/kg every 30 minutes for maintenance) were given to provide neuromuscular blockade.

Endotracheal intubation was performed using a cuffed tracheal tube with an internal diameter of 7, 8, or 9 mm, depending on the trachea size. The patients were mechanically ventilated with an anesthesia machine (Dräger Zeus, Lübeck, Germany) in volume-control mode with decelerating flow. Ventilation frequency was set to 10-14 breaths/min to achieve normocapnia. A tidal volume of 7 mL/kg and a positive end-expiratory pressure of 4 cmH_2O were applied. The fraction of inspired oxygen (FiO_2) was initially set to 0.5 and was increased to 0.8 after

CPB. Before CPB, the membrane oxygenator was primed with 1,500 mL of lactated Ringer's solution. Heparin was administered at a dose of 300 U/kg, with the activated clotting time maintained at >400 seconds. Moderate 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 restoring ventilation, the lungs were inflated three times to achieve a peak airway pressure of 30 cmH_2O, maintained at this pressure for three seconds to facilitate lung recruitment.

III.2.4. Characterization of gas exchange

Arterial and central venous blood samples were used to characterize gas exchange at each protocol stage. The partial pressures of oxygen and carbon dioxide in the arterial (PaO_2 and $PaCO_2$, respectively) and venous blood samples (PvO_2 and $PvCO_2$, respectively) were determined using a Radiometer ABLTM 505 (Copenhagen, Denmark). Blood samples were also used to measure oxygen saturation in arterial (SaO_2) and venous blood (SvO_2). The lung oxygenation index was calculated as PaO_2/FiO_2. The intrapulmonary shunt fraction (Qs/Qt) was calculated using the Berggren equation [102]:

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

Where CcO_2, CaO_2, and CvO_2 denote the oxygen content of the pulmonary capillary, arterial, and central venous blood, respectively. CcO_2 was calculated using the following equation, assuming that the O_2 saturation of hemoglobin in the pulmonary capillaries was 100%:

$$CcO2\ \left[\frac{ml}{dl}\right] = 1.34\frac{ml}{g}xHb\ [g/dl] + 0.0031xPAO_2\ [mmHg]$$

where 1.34 mL/g is the Hüffner constant, Hb is the hemoglobin concentration in grams, the total dry gas pressure was 713 mmHg, and the respiratory exchange ratio was 0.8. The alveolar oxygen tension (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 mechanical ventilation, a calibrated mainstream capnograph (Novametrix, Capnogard, Andover, MA) was introduced into the ventilation circuit, and a screen pneumotachograph (Piston Ltd., Budapest, Hungary) was used to record central airflow. Simultaneous 15-second recordings of the CO_2 and ventilation flow were digitized (sampling frequency 102.4 Hz) and analyzed using custom-made software [70, 103]. Volumetric capnograms were constructed from the CO_2 and integrated flow signals. Time capnograms, which are routinely displayed in clinical practice, were analyzed in the time domain.

The phase-3 slopes of the time (S3T) and volumetric (S3V) capnograms were determined by fitting a linear regression line to the last 60% of phase 3 [104, 105, 106]. To account for the absolute concentration of CO_2 in the expired gas, both S3T and S3V were normalized (Sn3T and Sn3V, respectively) by dividing each slope by the average value of the corresponding end-tidal CO_2 concentration in the mixed expired gas [107, 108, 109]. Additionally, the deadspace fraction was calculated from the volumetric capnograms. The physiologic deadspace fraction according to Bohr (VDB), which reflects the alveolar volume with decreased or no perfusion, was calculated from the capnograms as follows [110]:

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

Where $PACO_2$ is the average alveolar partial pressure of CO_2 measured at the midpoint of the third phase of the capnogram [111]. $PECO_2$ is the partial pressure of mixed exhaled CO_2, calculated by integrating the area under the volumetric capnogram curves and distributing the obtained values by the tidal volume (VT).

The physiologic deadspace calculated by Enghoff's approach (VDE) provides additional information on V/Q mismatch. Therefore, in addition to the VDB, the intrapulmonary shunt (i.e., alveolar volume with decreased or absent ventilation but maintained perfusion) was incorporated. VDE was calculated as follows [112]:

$$\frac{VDE}{VT} = \frac{(PaCO_2 - PECO_2)}{PaCO2}$$

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

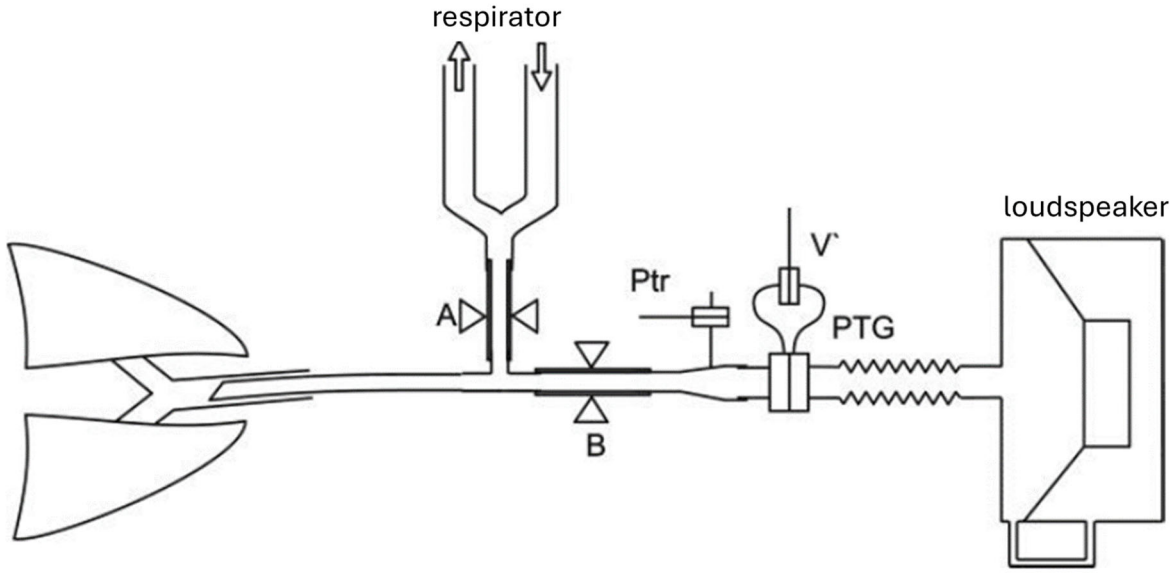

Figure 1. *Scheme of the measurement apparatus for the forced oscillations. „A" and „B" denotes the collapsible segments used to swith the patient between the respirator and the measurement apparatus. Ptr: tracheal pressure, V': tracheal airflow, PTG: pneumotachograph*

Dopamine-induced changes in the mechanical properties of the airways and lung tissues were assessed by measuring the low-frequency forced oscillatory input impedance of the lungs (ZL), as previously detailed [70, 71]. Briefly, a T-piece with two collapsible segments was attached to the distal tracheal tube, with one end connected to the respirator and the other end to a loudspeaker-in-box system. This apparatus made it possible to switch the patient from the respirator to the forced oscillatory setup during the measurements. The pseudorandom pressure excitations generated by the loudspeaker were introduced into the trachea during short (15-second) end-expiratory apneic pauses from mechanical ventilation. The forcing signal comprised 15 multiple integer components, with 0.4 Hz as the fundamental frequency, ranging between 0.4 and 6 Hz.

To measure tracheal airflow, a 28-mm internal diameter screen pneumotachograph was connected to a differential pressure transducer (ICS model 33NA002D; ICSensors, Milpitas, CA). An identical pressure transducer was used to detect tracheal pressure (Ptr). ZL was computed from the power spectra of Ptr and V'; the ensemble average was determined under each condition. The mean ZL data were fitted by a well-validated four-parameter model, which included frequency-independent airway resistance (Raw) and inertance (Iaw) and a constant-

phase tissue compartment characterized by the coefficients of damping (G) and elastance (H), minimizing the difference between the measured and modeled impedance values.

Raw represented the flow resistance of the bronchial tree, while Iaw was related to the mass of the gas in the airways; these parameters were corrected for the instrumental resistance and inertance of the measurement apparatuses, including the endotracheal tube [70, 71, 113]. The tissue parameters characterized the resistive (G) and elastic properties of the lung parenchyma (H).

III.2.7. Measurement protocol

Upon stabilization of the hemodynamic and respiratory mechanical conditions after midline sternotomy, measurements were performed five minutes before starting CPB (pre-CPB). These measurements included recordings of four capnogram traces, analyses of arterial and central venous blood gas samples, registration of the total resistance (R) and dynamic respiratory compliance displayed by the ventilator (C), and collection of four ZL data epochs. The measurements took approximately three minutes at each time point. The same set of data was collected five minutes after weaning from CPB, when stable circulatory and ventilator conditions were reestablished (post-CPB).

Subsequently, patients in the DA group received an intravenous infusion of dopamine at 3 µg/kg/min. Five minutes after initiating the dopamine infusion, the third data collection step was conducted in the same manner as detailed earlier (i.e., intervention: INT). The same timing and data collection procedures were followed for patients who did not require the administration of any inotropic or other vasoactive or bronchoactive drugs (control group).

III.2.8. Statistical Analyses

Scatters in measured variables were expressed as a 95% confidence interval of the mean. Normality of the data was checked with the Kolmogorov-Smirnov test with Lilliefors correction. Two-way repeated measures analysis of variance, with the inclusion of an interaction term, was used for all measured variables. To establish the effects of CPB and the subsequent administration of dopamine, the protocol stage was the within-subject factor (before CPB, after CPB, and after intervention), and group allocation was the between-subject factor (DA or control group). The Holm–Sidak multiple comparison procedure was adopted to compare the variables between the study groups at different protocol stages. Differences in the demographic, anthropometric, and clinical characteristics were assessed using a chi-square test.

Sample sizes were estimated to enable detection of a clinically relevant 25% difference in the primary outcome parameter of Raw after CPB. Accordingly, the analysis of variance test indicated that at least 45 patients in each group were required to detect a statistically significant difference, with an assumed variability of 10%, a power of 80%, and a significance level of 5%. The statistical tests were performed using the SigmaPlot software package (Version 14, Systat Software, Inc., Chicago, IL). All reported p-values were two-sided.

IV. Results

IV.1. Study I.

IV.1.1. Patient population

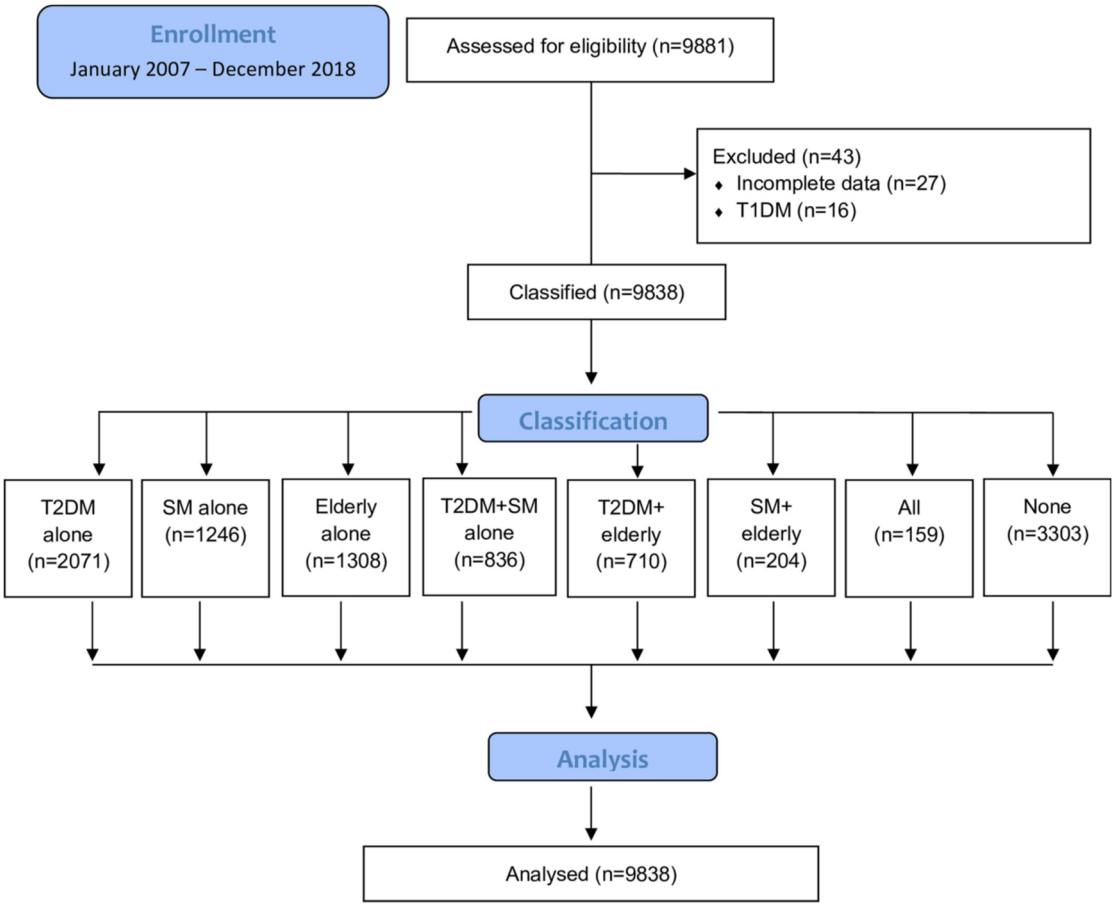

Figure 2. *Group allocation ana analyses of cardiac surgery patients with diabetes mellitus only (T2DM alone), smoking (SM alone), and ageing (Elderly alone). Groups containing pairwise (T2DM + SM, T2DM + Elderly, and SM + Elderly) and concomitant combination ("All") significant factors were also separated. "None" denotes no occurrence of these risk factors. The total of 9881 patients were enrolled in the study period. Forty-three patients were excluded from the data set due to incomplete registration of the anthropometric outcomes and/or blood sample analyses (n = 27), or subsequent to the diagnosis of type 1 diabetes (n = 16). As a result, 9838 cardiac surgery patients were included in the analyses.*

The involvement of patients in the retrospective data analyses and their group allocation is demonstrated in a CONSORT flow chart (Fig 2). A total of 9,881 patients were enrolled during the study period. Twenty-seven patients were excluded from the data analyses due to incomplete anthropometric data, blood pressure readings, or blood sample analyses. Additionally, 16 patients were diagnosed with type 1 diabetes and were excluded from the

analyses because of their fundamentally different diabetes phenotype compared to the main population, which included those with T2DM. These considerations resulted in the classification of 9,838 patients.

IV.1.2. Anthropometric data and clinical characteristics

	T2DM alone	**SM alone**	**Elderly alone**
N	2071	1246	1308
Gender (F/M)	1005/1066	327/918*	322/986*
Weight (kg)	84.4 ± 17*	77.5 ± 17	75.5 ± 13*
Height (cm)	165 ± 10	168 ± 9	165 ± 9
BMI (kg/m^2)	31.0 ± 5.5*	27.3 ± 5.2*	27.6 ± 4.3
Age (years)	65.5 ± 7.6	59.0 ± 9.3	78.1 ± 4.0
HbA1c (%)	6.97 ± 1.26*	5.85 ± 0.48	5.84 ± 0.68
Hb (mg/dL)	12.29 ± 1.72*	13.08 ± 1.70*	12.32 ± 1.75
AS/AI/AS&AI (n) (%)	373/90/43 (15.7/4.3/2.1)	165/41/15 (13.1/3.3/1.2)	349/50/27 (25.9/3.8/2.1)
MS/MI/MS&MI (n) (%)	19/139/7 (0.9/6.6/0.3)	10/90/4 (0.8/7.2/0.3)	3/80/9 (0.2/6.1/0.7)
AS&MI (n) (%)	30 (1.4)	10 (0.8)	20 (1.5)
AD/AAA (n) (%)	12/26 (0.6/1.3)	15/24 (1.2/1.9)	3/9* (0.2/0.7)
LAM (n) (%)	12 (0.6)	9 (0.7)	6 (0.5)
EI (n), (%)	60 (2.9)	33 (2.6)	29 (2.2)
GUCH (n), (%)	10* (0.5)	21* (1.7)	4* (0.3)
CAD (n), (%)	1016* (49.1)	721* (57.9)	503 (38.5)
CAD+MI (n), (%)	73 (3.5)	40 (3.2)	49 (3.7)
CAD+AS (n), (%)	266* (12.8)	71 (5.7)	213* (16.3)

Table 1*. Characteristics and diagnoses of cardiac surgery patients with diabetes mellitus only (T2DM alone), smoking (SM alone), and ageing (Elderly alone). Data for continuous variables are shown as mean ± SD; data for categorical variables are represented as number of patients in each group (top number in each cell) with percentage relative proportion rates (bottom numbers in each cell). * $p < 0.05$ vs. "None". AAA, aortic arch reconstruction; AD, aorta dissection; AI, aortic insufficiency; AS, aortic stenosis; BMI, body mass index; CAD, coronary artery disease; EI, endocarditis; GUCH, Grown-Up Congenital Heart Disease; Hb, hemoglobin; LAM, left atrial myxoma; MI, mitral insufficiency; MS, mitral stenosis; SM, smoking.*

	T2DM + SM	T2DM + Elderly	SM + Elderly	All	None
N	836	710	204	159	3303
Gender (F/M)	228/608*	144/566*	14/190*	12/147*	1572/1731
Weight (kg)	87.0 ± 18*	81.4 ± 14*	75.6 ± 13.3	81.8 ± 15.0*	77.6 ± 16.3
Height (cm)	168 ± 9	167 ± 9	169 ± 8	169 ± 8	166 ± 10
BMI (kg/m^2)	30.8 ± 5.7*	29.3 ± 4.4*	26.6 ± 4.0*	28.8 ± 4.8	28.1 ± 5.0
Age (years)	61.5 ± 7.5	77.3 ± 4.1	76.9 ± 4.1	76.6 ± 4.0	61.7 ± 12.5
HbA1c (%)	7.16 ± 1.65*	6.62 ± 1.0*	5.92 ± 0.45	7.28 ± 1.17*	5.63 ± 0.39
Hb (mg/dL)	12.78 ± 1.80	12.19 ± 1.73*	12.43 ± 1.82	12.09 ± 1.91	12.58 ± 1.64
AS/AI/AS&AI (n) (%)	93/16/9 (10.9/1.9/1.1)	146/29/13 (20.6/4.1/1.8)	43/2/2 (21.1/1/1)	24/7/2 (15.1/4.4/1.3)	712/184/78 (21.2/5.6/0.2)
MS/MI/MS&MI (n) (%)	2/46/2 (0.2/5.4/0.2)	6/27/0 (0.8/3.8/0)	0/10/1 (0/4.9/0.5)	1/7/0 (0.6/4.4/0)	32/401/21 (1.0/12.1/0.6)
AS&MI (n) (%)	5 (0.6)	6 (0.8)	3 (1.5)	1 (0.6)	36 (1.1)
AD/AAA (n) (%)	21/2* (2.5/0.2)	1/7 (0.1/1)	4/3 (2/1.5)	2/1 (1.3/0.6)	49/72 (1.5/2.2)
LAM (n) (%)	1 (0.1)	1 (0.1)	0 (0)	0 (0)	35 (1.1)
EI (n), (%)	21 (2.5)	16 (2.3)	3 (1.5)	6 (3.8)	105 (3.2)
GUCH (n), (%)	1* (0.1)	0* (0)	0 (0)	0 (0)	143 (4.3)
CAD (n), (%)	522* (62.4)	325* (45.8)	102* (50)	85* (53.5)	1178 (35.7)
CAD+MI (n), (%)	37 (4.4)	16 (2.3)	5 (2.5)	4 (2.5)	91 (2.8)
CAD+AS (n), (%)	69 (8.3)	147* (20.7)	29* (14.2)	26* (16.4)	238 (7.2)

Table 2. *Characteristics and diagnoses of cardiac surgery patients with pairwise (T2DM + SM, T2DM + Elderly, and SM + Elderly) and concomitant combination ("All") significant factors. "None" denotes no occurrence of these risk factors. Data for continuous variables are shown as mean ± SD; data for categorical variables are represented as number of patients in each group (top number in each cell) with percentage relative proportion rates (bottom numbers in each cell). * $p < 0.05$ vs. "None". AAA, aortic arch reconstruction; AD, aorta dissection; AI, aortic insufficiency; AS, aortic stenosis; BMI, body mass index; CAD, coronary artery disease; EI, endocarditis; GUCH, Grown-Up Congenital Heart Disease; Hb, hemoglobin; LAM, left atrial myxoma; MI, mitral insufficiency; MS, mitral stenosis; SM, smoking.*

	Number of cardiac surgery patients	AS/AI/ AS&AI/ AS&MI	MS/MI/ MS&MI	AD/ AAA	CAD, CAD+MI, CAD+AS	LAM, EI, GUCH
January	970	16.8%	5.2%	43.2%	32.9%	2.0%
February	857	16.5%	7.0%	42.9%	32.0%	1.7%
March	878	18.3%	5.7%	43.2%	30.9%	2.1%
April	911	18.3%	6.1%	42.2%	31.1%	2.5%
May	893	17.8%	6.9%	42.1%	31.5%	1.8%
June	921	17.4%	7.0%	43.0%	30.3%	2.4%
July	644	17.9%	5.0%	43.4%	31.5%	2.3%
August	509	18.0%	4.1%	43.1%	32.4%	2.5%
September	896	19.3%	5.6%	43.0%	29.4%	2.8%
October	890	18.7%	6.4%	41.8%	31.1%	2.1%
November	840	18.0%	6.6%	42.7%	30.2%	2.6%
December	628	16.8%	5.9%	43.3%	32.0%	2.1%
Total	**9837**	**17.8%**	**6.0%**	**42.8%**	**31.2%**	**2.2%**

Table 3. *Total number of cardiac surgery patients included in the data analyses (grey column), and relative number of cardiac surgery patients with different diagnoses (last 5 columns). Data show no significant seasonality; only the holyday seasons show a decrease in the number of patients due the limited availability of human resources available at the university hospital. No significant difference was observed between the months in the relative frequency of different diagnoses.*

The anthropometric data and main clinical characteristics of the study groups, based on significant factors exhibiting seasonal variations in the overall proportion of surgeries, are summarized in Tables 1 and 2. In line with the global proportion of cardiac surgery patients with T2DM (30%-40%) [21], 38.4% of patients in this study were diagnosed with T2DM. As expected, HbA1c levels were significantly higher in patients with diabetes (7.75±1.17) compared to those without metabolic disorders (5.69±0.4). The study population had a predominance of males (63.1%), a trend that persisted in each subgroup, except for patients with T2DM alone (51.4%) and those without examined risk factors (52.4%).

T2DM was significantly associated with 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 lower BMI (27.1 kg/m²; $p<0.001$). Compared to patients without risk factors, aortic diseases were more frequent in elderly patients ($p<0.05$), whereas the prevalence of grown-up congenital heart diseases was lower in patients with T2DM, smokers, and elderly patients ($p<0.05$). The proportion of coronary disease was generally higher in patients with T2DM and smokers ($p<0.05$).

The total number of cardiac surgery patients included in the data analyses for each month is shown in Table 3. These data indicate no significant seasonality; only the holiday seasons showed a decrease in the number of patients due to limited human resources at the university hospital. However, the relative frequency of various diagnoses did not differ between months.

IV.1.3. Seasonal variabilities: significant risk factors

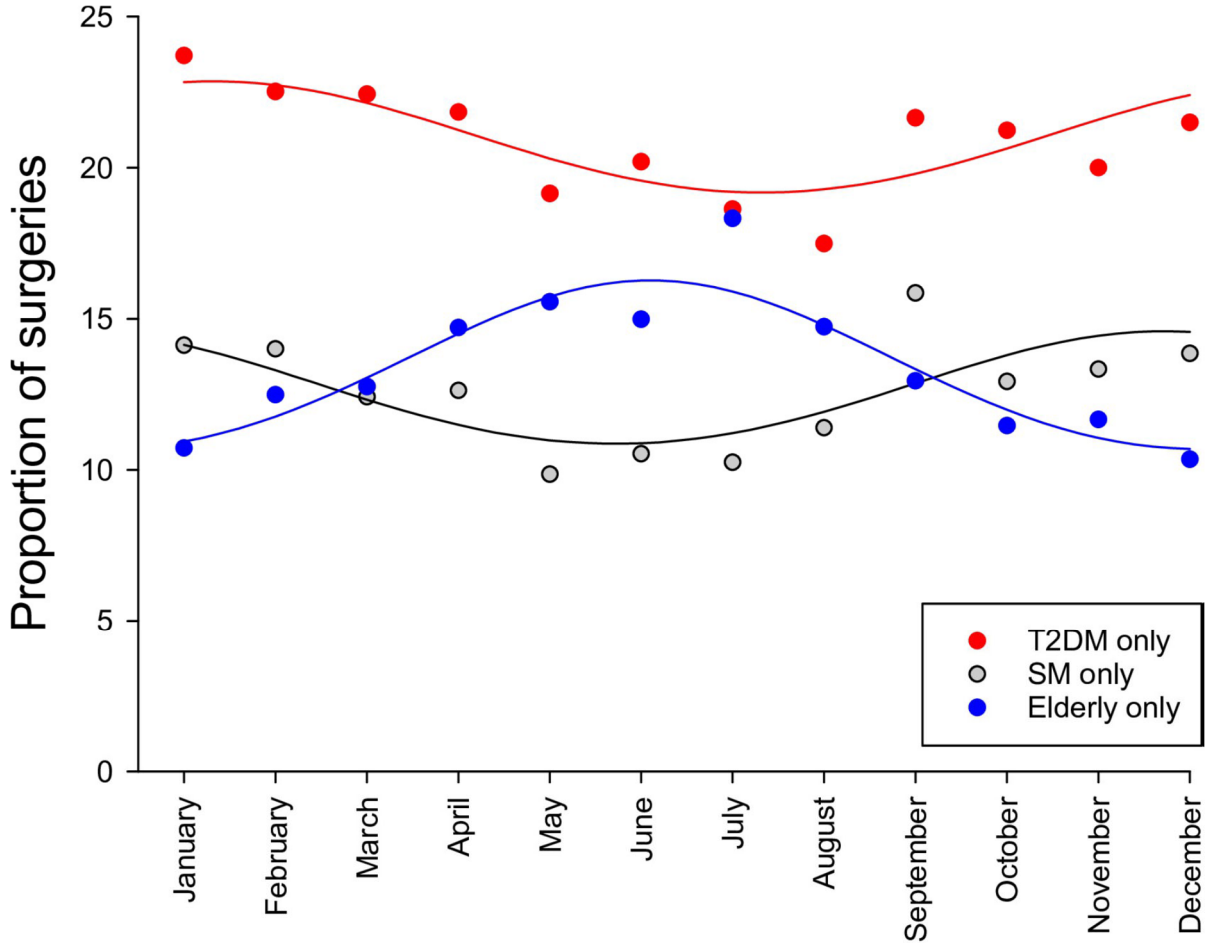

Figure 3. *Seasonal changes in the proportion of surgeries associated with type 2 diabetes mellitus (T2DM only), smoking (SM only), and ageing (Elderly only) for the monthly aggregated data over the 12-year study period (January 1, 2007 to December 31, 2018).*

There were no statistically significant seasonal variations for gender ($p = 0.81$) and BMI ($p = 0.75$); therefore, these variables were not included in further analyses. The main types of heart disease with sufficient patient numbers to analyze seasonal changes showed no statistically significant periodicity ($p = 0.30$, $p = 0.58$, $p = 0.51$, and $p = 0.75$ for aortic stenosis, mitral insufficiency, coronary artery disease, and coronary artery disease with mitral insufficiency, respectively). Conversely, statistically significant seasonal variations for the monthly aggregated data were observed for T2DM ($p<0.02$), smoking ($p<0.001$), and elderly ($p<0.001$) patients alone. Therefore, further analyses focused on these significant variables, including their pairwise and combined coexistence.

Seasonal patterns of statistically significant factors (T2DM alone, smoking alone, and ageing alone) for the monthly aggregated data over the 12-year study period are shown in Fig 3. The proportion of cardiac surgeries in patients with T2DM or who smoked peaked during the winter

months and decreased in the summer. Conversely, the seasonal peak for elderly patients was observed in the summer and was lowest in the winter months.

Seasonal variations in the proportion of cardiac surgeries for patients with paired combinations of significant factors are shown in Fig 4. No statistically significant seasonal variations were observed in elderly patients with T2DM ($p = 0.66$) or smoking ($p = 0.46$). However, the apparent seasonal variations of T2DM and smoking were additive, resulting in a marked and statistically significant effect, with peak occurrences of these patients in winter and lower occurrences in the summer months.

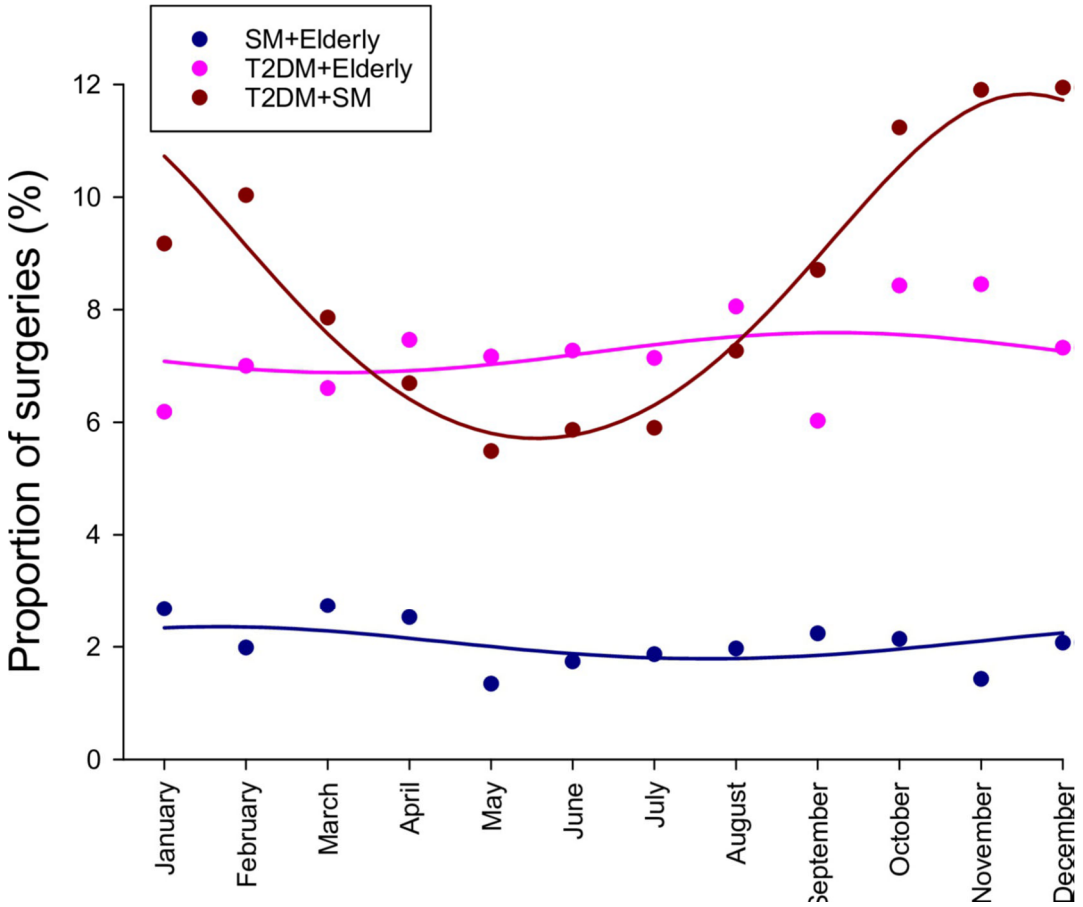

Figure 4. *Seasonal changes in the proportion of surgeries associated with combined smoking and ageing (SM + Elderly), type 2 diabetes mellitus and ageing (T2DM + Elderly), and type 2 diabetes mellitus and smoking (T2DM + SM) for the monthly aggregated data over the 12-year study period (January 1, 2007 to December 31, 2018).*

Table 4 summarizes the main parameters of the seasonal variations observed for the statistically significant individual factors (T2DM, smoking, and ageing) and their combination (T2DM and smoking) that demonstrated statistically significant seasonality ($p<0.001$). The goodness of fit for a simple harmonic trend to the data was excellent (>0.9) for the seasonality in T2DM, elderly, and smoking T2DM patients who underwent cardiac surgery. Although the model fit

was worse for seasonal changes in smoking-only patients, a highly significant periodic trend was still observed.

The proportion of cardiac surgery patients with T2DM and smoking peaked in January and December, respectively, whereas elderly patients most frequently underwent cardiac surgeries in June. To express the magnitude of seasonal differences in the observed risk factors for cardiac surgery, the amplitudes of each factor relative to the mean rate ([peak—mean]/mean) and to the nadir ([peak—nadir]/nadir) were calculated. The greatest seasonal variability was observed for the relative proportion of smoking patients with T2DM, with values indicating that the rate of such patients at the cardiac surgery unit was more than double in November compared to May. The magnitude of seasonal variations in the proportion of cardiac surgeries associated with elderly, smoking, and T2DM patients was lower but still demonstrated a markedly increased relative risk for cardiac surgeries during the corresponding peak periods.

	T2DM alone	**SM alone**	**Elderly alone**	**T2DM+SM**
Significance	$p = 0.0184$	$p<0.001$	$p<0.001$	$p<0.001$
Goodness of fit	0.92	0.51	0.95	0.97
Peak (month)	January	December	June	November
Nadir (month)	July	May	December	May
(peak–mean)/mean (%)	9.6	16.4	20.3	42.6
(peak–nadir)/nadir (%)	19.2	34.3	52.1	107.0
Maximum increase in proportion of cardiac surgeries (month)	October	August	March	September

Table 4. *Parameters characterizing seasonality for statistically significant variables. The maximum increase in the rate of heart surgery related to different pathologies refers to the peak of the first derivative of the fitted seasonality curves. T2DM: type 2 diabetes mellitus; SM: smoking.*

IV.1.4. Risk factors for cardiovascular complications

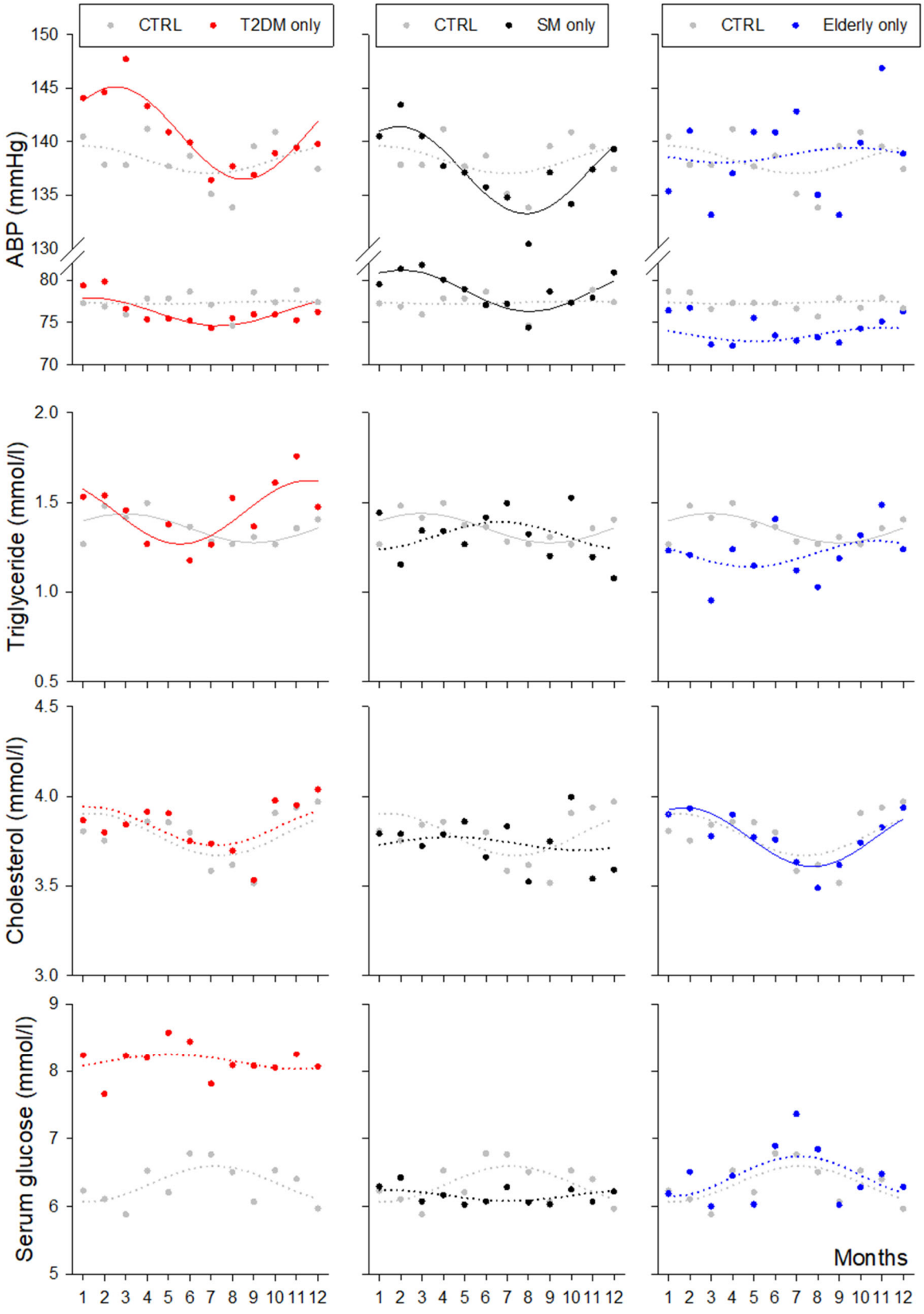

Figure 5. *Seasonal variations in the arterial blood pressure (ABP), serum triglyceride, total cholesterol and serum glucose levels in patients with type 2 diabetes mellitus (T2DM only, red)), smoking (SM only, black), and ageing (Elderly only, blue) for the monthly averaged data over the 12-year study period (January 1, 2007 to December 31, 2018). Grey symbols: non-elderly control patients scheduled for cardiac surgery without diabetes and smoking. Solid lined: statistically significant seasonality ($p<0.05$), dotted lines: no statical significant seasonal change.*

Figure 5 demonstrates the seasonal variations in potential risk factors for cardiovascular complications, such as systolic and diastolic arterial blood pressure, and serum levels of triglycerides, total cholesterol, and glucose in patients with significant factors for seasonal changes (T2DM alone, smoking alone, and ageing alone). Averaging data over the 12-year study period revealed significant seasonal changes in systolic ([peak-nadir]/nadir: 6.1%, $p<0.001$, with a peak in February-March) and diastolic blood pressures (4.4%, $p<0.05$, with a peak in January) and serum triglycerides in diabetic patients (17.1%, $p<0.005$, with a peak in December).

Significant seasonal variations were also observed in systolic and diastolic blood pressures in smoking patients (6.1% and 6.5%, respectively, $p<0.001$ for both, with peaks in February), and serum cholesterol in elderly patients (9.1%, $p<0.001$, with a peak in February).

IV.2. Study II.

IV.2.1. Patient population

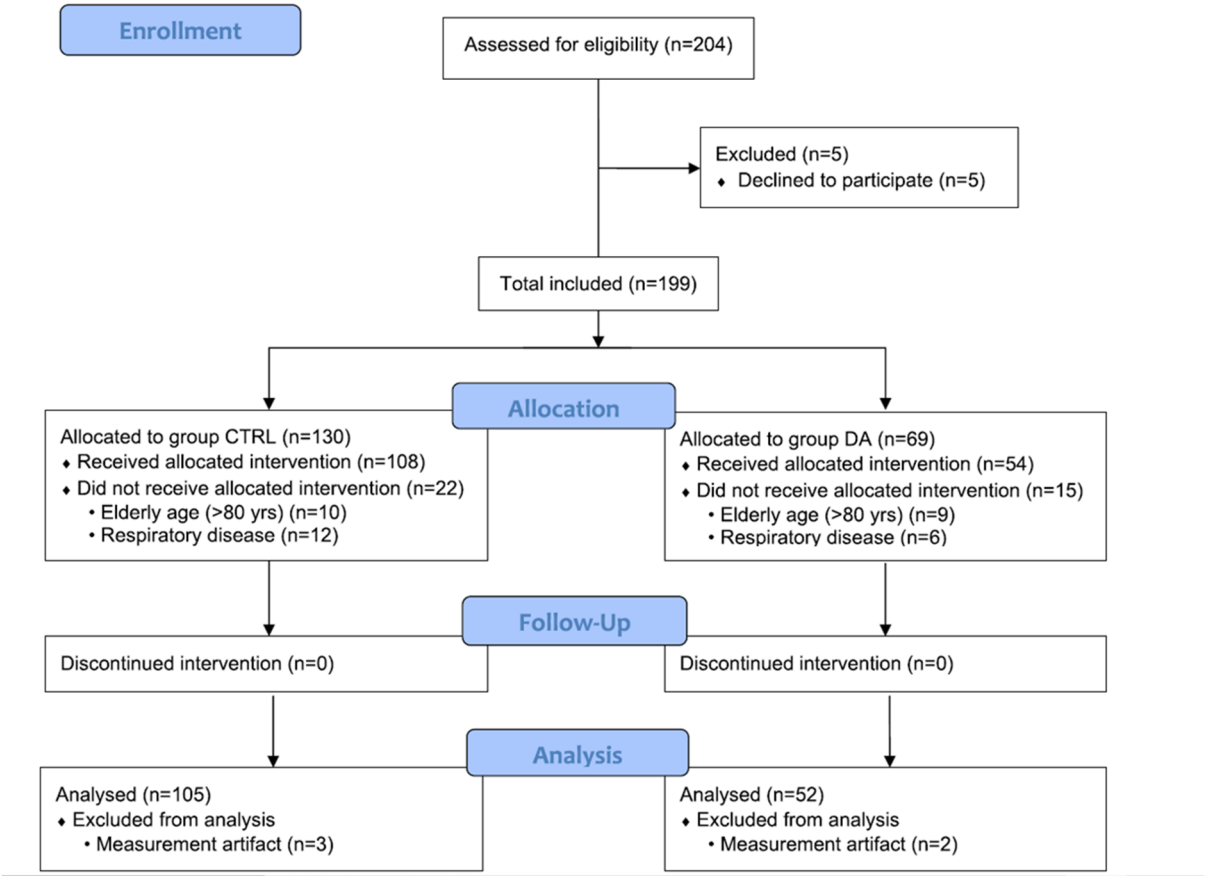

***Figure 6**. CONSORT flow diagram for the dopamine study (Study II).*

Based on the clinical need to support cardiac function with a positive inotrope, patients were assigned to either the dopamine group (DA, n = 52) or the control group (control, n = 105). The administration of dopamine and the allocation of patients to the DA group were based on a clinical decision algorithm using multimodal monitoring approaches. The main factors in this process included the patients' history and clinical parameters during weaning from cardiopulmonary bypass (CPB), such as central venous pressure (>8-10 mmHg), mean arterial pressure (<65 mmHg), central venous oxygen saturation (<70%-75%), and the contractility of the left and right ventricles estimated visually in the open chest or assessed by transesophageal echocardiography. Patients over 80 years of age and those with doctor-diagnosed chronic respiratory diseases were excluded. Additionally, patients receiving high doses of dopamine, dobutamine, epinephrine, milrinone, or an intra-aortic balloon pump intraoperatively were not included in the study population. Figure 6 shows the flow of participants through the various stages of the trial.

IV.2.2. Anthropometric data and group allocations

Group	Group CTRL (n = 105)	Group DA (n = 52)
Male/female	67/38	32/20
Age, y	63 ± 11	65 ± 12
Height, cm	167 ± 9	168 ± 9
Weight, kg	79 ± 12	82 ± 11
Left ventricular EF	58.2 ± 10.8	54.0 ± 11.7
Left atrial dimensions, mm	49 ± 8 × 50 ± 8 × 60 ± 7	53 ± 12 × 52 ± 8 × 61 ± 9
EuroSCORE	4.2 ± 2.0	5.7 ± 2.1*
Postoperative inotropic medication	43.9	80.9*
Patients, %	3.7 ± 2.2	5.7 ± 6.2*
dose, μg/kg/min		
Postoperative vasoconstrictor use	3.2	11.1*
% of patients		
Surgery AVR/AVP	38	17
Surgery AVR + CABG	33	17
Surgery MVR/MVP	17	7
Surgery MVP + CABG	8	7
Other surgery	9	4
Redo surgery, % of patients	3.2	2.2
Duration of CPB, min	101 ± 31	90 ± 27*
Intraoperative blood loss, ml	1050 ± 575	1065 ± 536
Postoperative blood loss, ml	651 ± 830	511 ± 472

Table 5. *Demographic, anthropometric, and clinical characteristics of the patients involved in Study II. Anthropometric data are presented as mean § 95% confidence interval. Other surgery included left atrial myxoma removal, atrial septal defect closure, and ascending aorta aneurysm repair. Abbreviations: AVP, aortic valve plasty; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; EF, ejection fraction; MVP, mitral valve plasty; MVR, mitral valve replacement. * $p < 0.05$ between groups.*

Table 5 summarize the sex, age, height, body weight, and the parameters related with the surgery types did not significantly differ between the protocol groups.

IV.2.3. Lung mechanical parameters

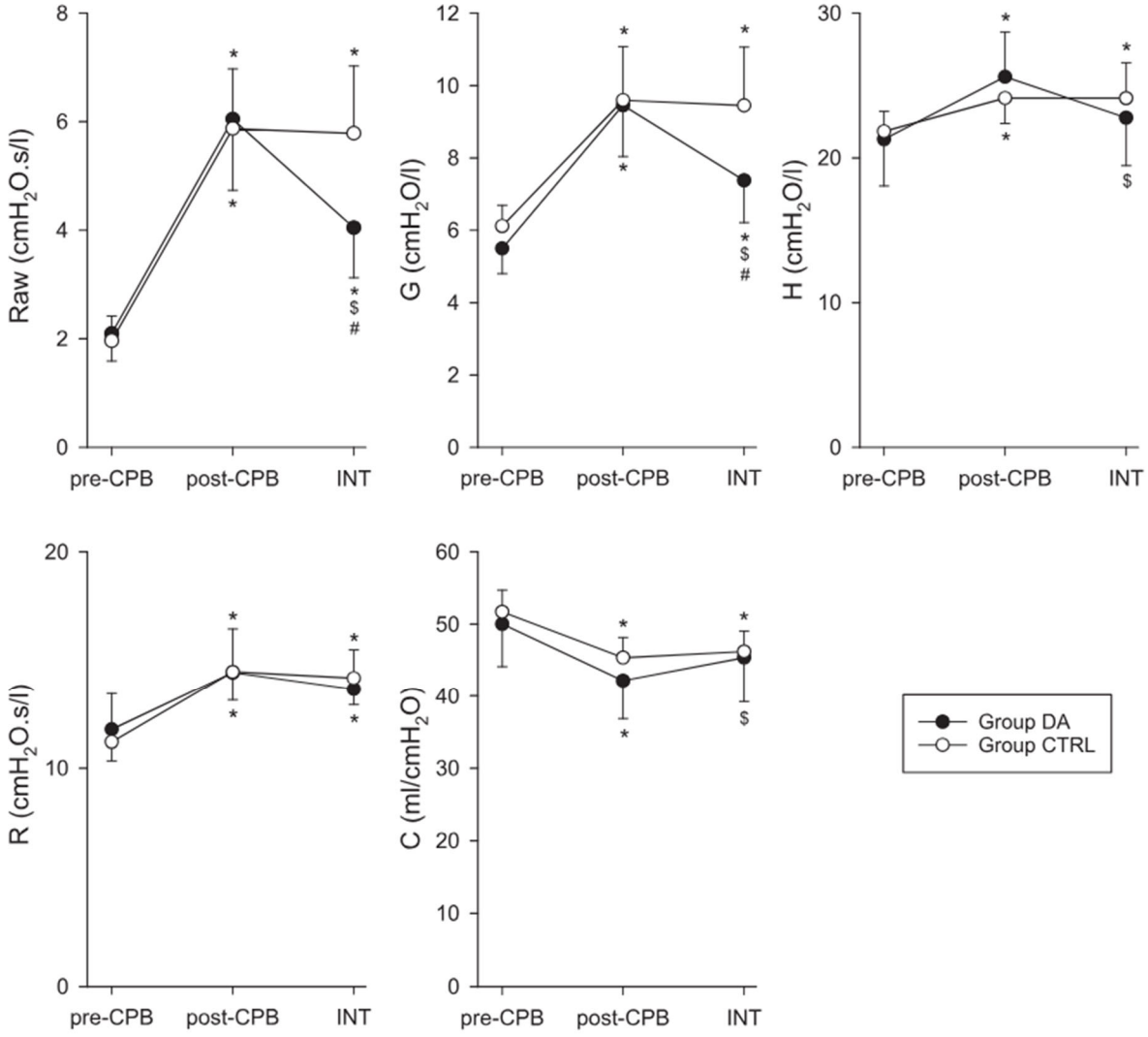

Figure 7. *Mean (symbols) with 95% confidence interval (error bars) of the forced oscillatory airway resistance (Raw) and lung tissue damping (G) and elastance (H) in patients treated with 3 µg/kg/min of dopamine (DA group, n = 52) and in patients who did not receive the inotrope (control group, n = 105); *: p < 0.05 vs. preCPB condition within a group. $: p < 0.05 vs. post-CPB condition within a group; #: p < 0.05 between the protocol groups within a stage. CPB, cardiopulmonary bypass; INT, intervention.*

Figure 7 demonstrates the airway and lung tissue mechanical parameters at different protocol stages in both study groups included in Study II. CPB induced marked and significant changes in Raw and G, and smaller but significant changes in H, R, and C, with no difference between the protocol groups in the magnitude of CPB-induced changes ($p < 0.001$ for all). Patients in the control group exhibited no significant changes in any of the measured parameters after CPB. Conversely, patients in the DA group had significantly decreased Raw, G, and H ($p < 0.001$ for all) but no significant changes in R and C on the ventilator display.

IV.2.4. Capnogram shape factor and dead space parameters

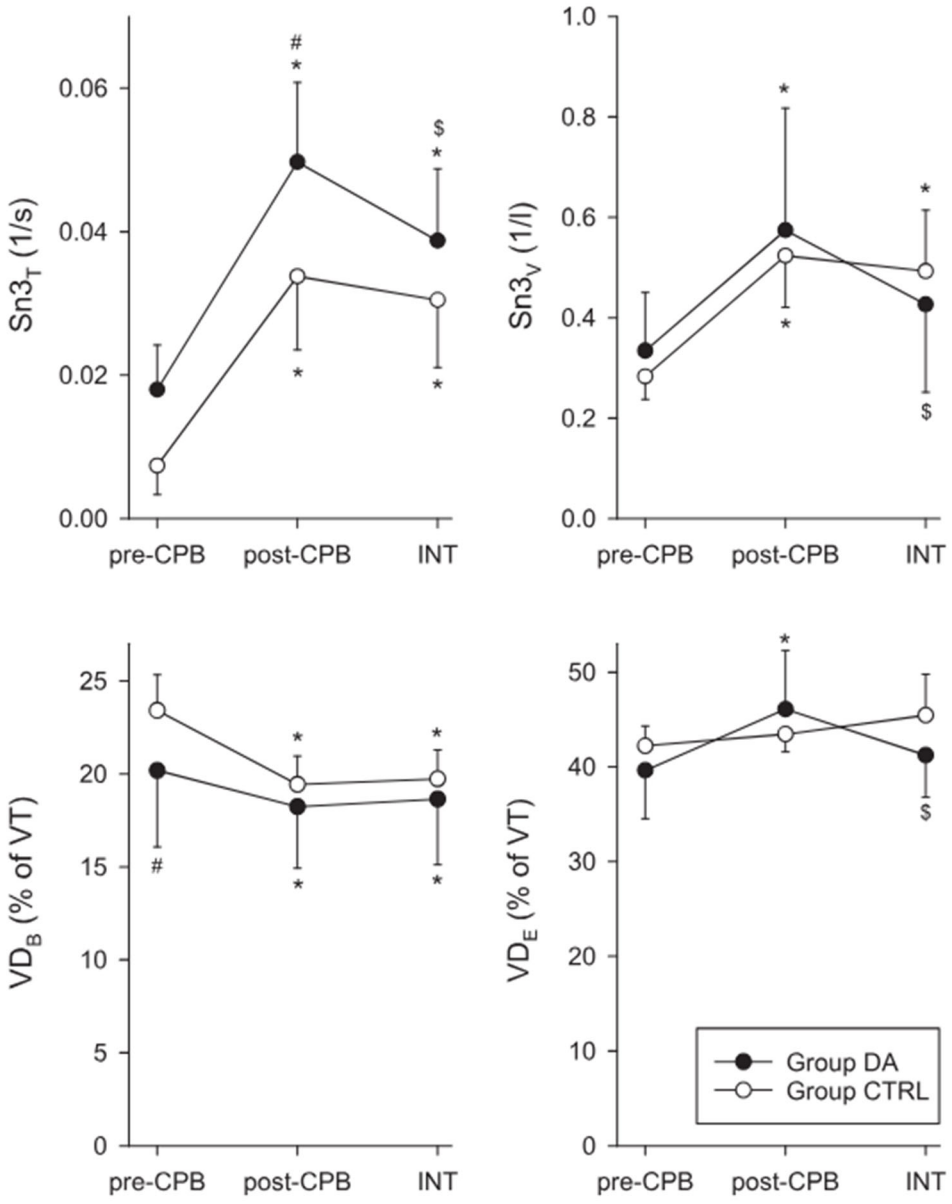

Figure 8. *Mean (symbols) with 95% confidence interval (error bars) of the normalized phase-3 slope of time (Sn3T) and volumetric capnograms (Sn3V) and the ventilation deadspace fractions according to Bohr (VDB) and Enghoff (VDE) in patients treated with 3 µg/kg/min of dopamine (DA group, n = 52) and in patients who did not receive the inotrope (control group, n = 105). Error bars represent standard deviations; *p < 0.05 vs. pre-CPB condition within a group. $ p < 0.05 vs. post-CPB condition within a group; # p < 0.05 between the protocol groups within a stage. CPB, cardiopulmonary bypass; INT, intervention.*

The normalized shape factors and deadspace parameters obtained by time and volumetric capnography are summarized in Figure 8. Elevations in Sn3T and Sn3V after CPB were

associated with decreases in VDB in both groups ($p < 0.001$ for both), whereas VDE was elevated only in the DA group ($p < 0.005$). The DA group had significantly decreased Sn3T, Sn3V, and VDE ($p < 0.01$ for all) but no detectable change in VDB. In the control group, the corresponding changes in any of these parameters did not reach statistical significance in the intervention period (post-CPB versus INT).

IV.2.5. Gas exchange and intrapulmonary shunt

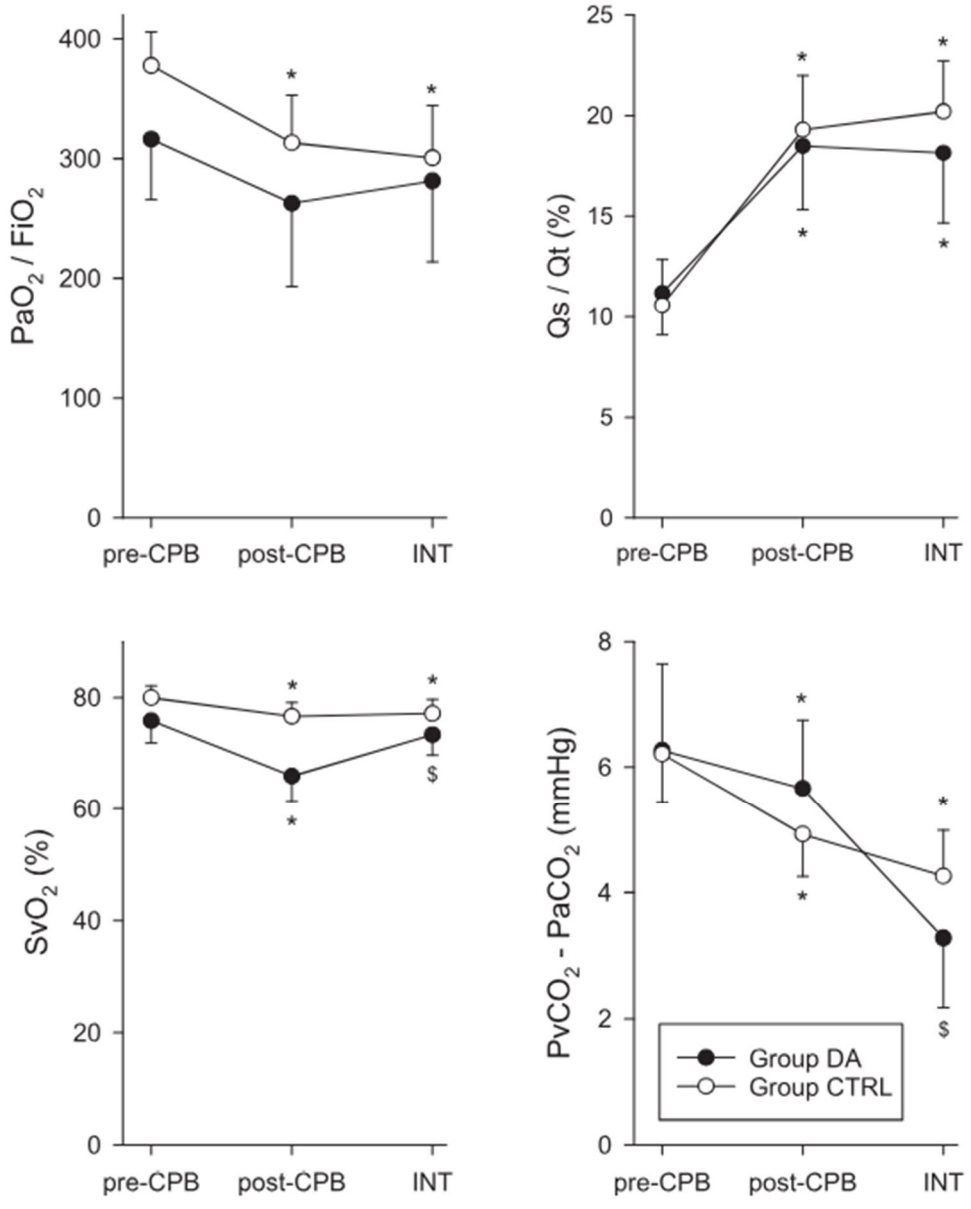

Figure 9. *Mean (symbols) with 95% confidence interval (error bars) of the lung oxygenation index (PaO2/FiO2), intrapulmonary shunt (Qs/Qt), venous oxygen saturation (SvO2), and venoarterial carbon dioxide difference (PvCO2-PaCO2) in patients treated with 3 µg/kg/min of dopamine (DA group, n = 52) and in patients who did not receive the inotrope (control group, n = 105).*

*Error bars represent standard deviations; *: $p < 0.05$ vs. pre-CPB condition within a group. $: $p < 0.05$ vs. post-CPB condition within a group; #: $p < 0.05$ between the protocol groups within a stage. CPB, cardiopulmonary bypass; INT, intervention.*

The changes in the parameters associated with oxygenation and intrapulmonary shunt are demonstrated in Figure 9. In both groups, CPB significantly decreased the PaO_2/FiO_2, increased the Qs/Qt, and decreased the SvO_2 and $PvCO_2$-$PaCO_2$ ($p < 0.001$ for all). In the DA group, there were no significant detectable changes in PaO_2/FiO_2 and Qs/Qt, but there was a significant increase in SvO2 and a significant decrease in $PvCO_2$-$PaCO_2$ ($p < 0.001$ for both).

V. Discussion

V.1. Study I.

In this study, we analyzed the medical records of all consecutive adult patients over a 12-year period at the cardiac surgery unit in our tertiary-care university hospital. Our analyses revealed that the monthly proportion of patients undergoing cardiac surgery with diabetes, smoking, and elderly age exhibited seasonal variation. Non-elderly patients with diabetes and/or smoking showed a peak proportion rate during the winter, whereas heart surgery in elderly patients without diabetes and smoking was most frequently required in the summer. The concomitant occurrence of diabetes and smoking had an additive effect on the proportion of cardiac surgeries associated with these pathologies, while the simultaneous presence of older age and diabetes or smoking eliminated the seasonal variation.

V.1.1. Methodological considerations

Emphasis was placed on the accuracy and adequacy of data registration. The risk factors examined for seasonal changes (diabetes, smoking, and elderly age) were identified based on objective and internationally well-defined diagnostic criteria. Data registration was performed by a stable staff of clinicians, including five specialized anesthesiologists, throughout the study period on the day prior to surgery. Since the standard practice at our institution is to avoid waiting lists longer than five days, the seasonal trends observed in this study accurately reflect the worsening and exacerbation of cardiovascular diseases requiring surgical intervention.

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

One of the main findings of this study was a significant increase in the proportion of cardiac surgeries associated with diabetes during the coldest months of the year. The sinusoidal seasonal trend suggested that the relative risk for patients with diabetes undergoing cardiac surgery during the winter is almost 20% higher than in the summer (Fig. 3 and Table 3). In patients with diabetes, hyperglycemia leads to endothelial dysfunction, resulting in low-grade inflammatory, prothrombotic, proliferative, and vasoconstrictive processes [114]. These mechanisms may converge and lead to hypertension, atherosclerotic cardiovascular disease, and heart failure [115, 116, 117]. Hypertension can be exacerbated in a cold environment[56, 118, 119], increasing myocardial workload and oxygen demand, or worsening functional valve insufficiencies. In addition to these mechanisms, viral infections [120] and/or vitamin

deficiency [121] may also play a role. This seasonality is reflected in the high seasonal variation in serum glucose levels [122] and the incidence rates of type 1 [120] and T2DM [123, 124] uring the coldest months. The systolic and diastolic blood pressures at admission, along with serum triglycerides, were significantly higher in the present T2DM cohort in January than in July over the 12-year study period (Fig. 5). Severe manifestations of these pathologies require surgical intervention more frequently during winter for coronary and aortic valve diseases (Table 1).

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

The proportion of smoking patients undergoing cardiac surgeries without T2DM or advanced age was lower than those with T2DM alone in our population. However, since the seasonal changes were similar in smoking patients and patients with T2DM only, the relative peak-to-peak seasonal variability reached 34% (Fig. 3 and Table 3). Similar to T2DM, smoking is characterized by a blunted response to endothelium-dependent vasodilators due to diminished bioavailability of nitric oxide [125]. Therefore, mechanisms triggered by endothelial dysfunction and subsequent elevated vascular tone may be responsible for the seasonal variations observed in smoking patients within the cardiac surgery population.

Common pathophysiological processes in T2DM and smoking responsible for the seasonality were confirmed by the additive effect of these factors, as reflected in the systolic and diastolic blood pressures during the coldest season (Fig. 5). Consequently, the relative peak-to-peak seasonal variability reached more than 100% in smoking patients with diabetes (Fig. 4 and Table 3).

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

Further significant seasonal variability was observed in the cardiac surgery cohort for elderly patients without T2DM or smoking, with peak-to-peak seasonal variability exceeding 50% (Fig. 3 and Table 3). Unlike smoking and T2DM patients, the proportion of elderly patients undergoing cardiac surgeries peaked in summer. This opposite trend in morbidity may be attributed to the compromised elasticity of large conductive arteries [126]. The stiffening of large arteries makes elderly individuals more susceptible to hypovolemia and hypotension [127]. While seasonal variations were masked by the multifactorial comorbidities of this elderly

cohort, the significantly lower diastolic blood pressure observed in the summer months (73.1 mmHg in June-August) compared with the winter season (76.5 mmHg in December-February, $p<0.05$) aligns with previous findings, indicating that the exacerbation of symptoms is expected to be more frequent during the warmest season.

V.1.5. Effects of combined cardiovascular risk factors

Interestingly, seasonal variability disappeared when ageing was associated with diabetes or smoking (Fig. 4). The lack of seasonality in these comorbidities may be attributed to the superposition of two sinusoidal waves of ageing and diabetes or smoking. Since these waves have similar periods but opposite phases, the periodicity is eliminated. While the lack of season-dependent periodicity in these patients mimics an invariable monthly proportion, these patients are still exposed to the individual risk factors of ageing, diabetes, and smoking.

V.1.6. Effects of other factors on epidemiology

There was no evidence of seasonal changes in the proportion of patients undergoing surgeries for specific heart diseases (i.e., aortic stenosis, mitral insufficiency, or coronary artery disease) for the entire population. Seasonal variation may be related to peripheral vasculature sensitivity to temperature changes rather than the type of cardiac disease. This suggests that diabetes, smoking, and ageing are the primary season-dependent factors regardless of the nature of heart pathology. Gender and BMI do not directly affect the peripheral vasculature, as these factors exhibited no seasonal variation.

V.1.7. Seasonal temperature pattern

An important feature of our findings is related to the local climate. Hungary is situated in East-Central Europe and has four seasons with a continental climate. The Hungarian Meteorological Service calculated the average monthly temperature from daily averages, which varied between 0.7°C (33.3°F) in January and 23.1°C (73.6°F) in July during the 12-year study period in our region (Fig. 10). Our findings may represent the seasonal changes of cardiovascular comorbidities of diabetes, smoking, and ageing in the temperate climate zone of the world, where the majority of the human population resides.

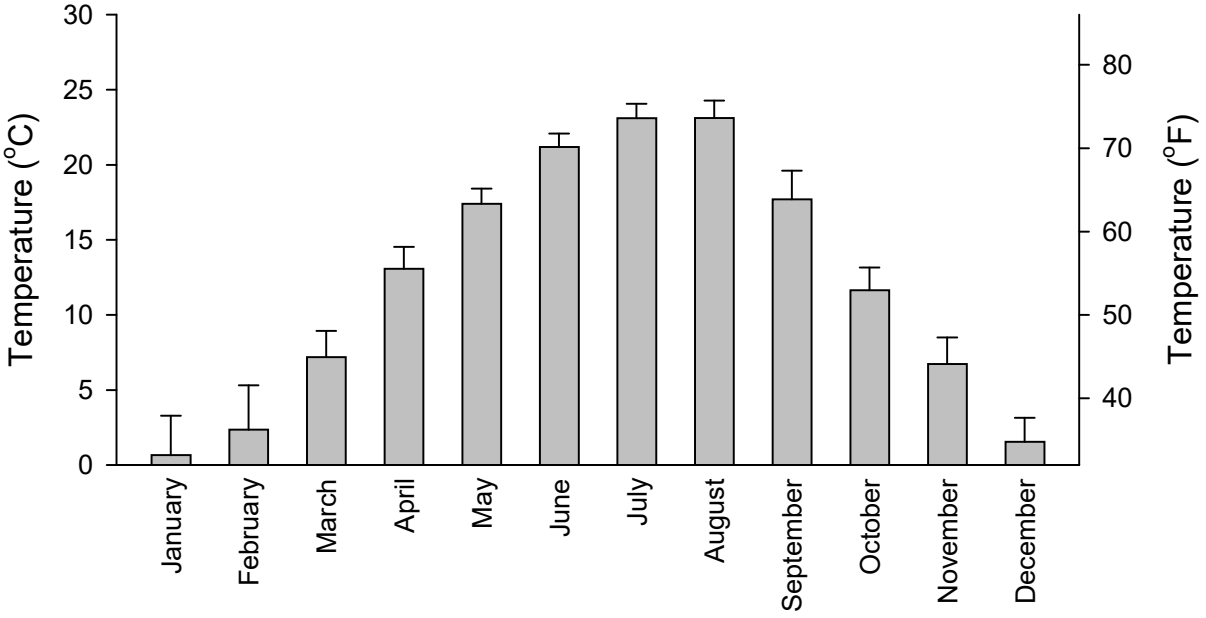

Figure 10. *Monthly temperature (mean and SD) calculated from the daily averages according to the Hungarian Meteorological Service for the 12-year study period (January 1, 2007 to December 31, 2018) in South-East Hungary.*

V.1.8. Study limitations

Some limitations related to the present findings warrant consideration. The Hungarian health insurance system provides benefit coverage to all citizens, and free medication is available for low-income patients. These factors mitigate the influence of financial background on patient care. However, continuous health monitoring may be less rigorous in some patients with social negligence, which could bias the cardiovascular effects of diabetes. This bias is expected to play a minor role in our findings due to the involvement of a large cohort over an extended period.

Nevertheless, generalizing our findings to other regions with different social and healthcare systems requires consideration of local socioeconomic factors, as well as national and institutional scheduling policies.

V.2. Study II.

In this large cohort of patients who underwent cardiac surgery with CPB, we observed that dopamine's ability to improve airway and lung tissue mechanics was associated with its benefit on V/Q matching. The importance of this study stems from the fact that previous research

reported that the beneficial effects of dopamine on airway function might be associated with potentially deleterious consequences on V/Q matching. Forced oscillatory measurements demonstrated dopamine's ability to reverse detrimental lung function changes induced by extracorporeal circulation. Additionally, capnography and blood gas measurements revealed that these mechanical changes were associated with improvements in V/Q matching and dead space ventilation without any detrimental consequences on lung oxygenation or intrapulmonary shunt.

V.2.1. Effects of CPB

The systemic inflammatory response after CPB leads to pathophysiologic changes, ranging from mild organ dysfunction to multisystem organ failure, with the lungs being one of the most commonly affected organs [128, 129]. Accordingly, prominent bronchoconstriction following CPB was observed. This airway pathology was associated with moderate but significant deteriorations in the viscoelastic properties of the lung tissue (Fig. 7), which can be attributed to intrinsic alterations in lung tissue properties and/or atelectasis development. The forced oscillatory airway and tissue changes were more sensitive compared to the observations in the resistance and compliance displayed by the ventilator. This apparent discrepancy can be explained by the inclusion of instrumental resistance in R, which blunted the CPB-induced changes in airway resistance [113]. Although the current results on the effects of CPB on lung mechanics were in accordance with those reported previously [70, 71, 130], the underlying pathophysiologic mechanisms have not been fully clarified. Airway narrowing due to mucosal thickening, along with the endogenous release of mediators and/or inflammatory cytokines that can cause bronchoconstriction, may be implicated as the mechanism [128, 129, 131]. Deterioration in lung tissue viscoelasticity after CPB can be a consequence of intrinsic changes in the dissipative and elastic properties of the pulmonary parenchyma secondary to interstitial edema formation [72], in addition to persistent alveolar derecruitment, leading to heterogeneous loss of ventilated lung volume [132].

The association of adverse lung mechanical changes after weaning from CPB with increased normalized phase 3 slopes on the time and volumetric capnograms indicated impairment of alveolar emptying and/or V/Q matching (Fig. 8). Notably, the Sn3T value tended to be greater in the DA group than in the control group, which can be attributed to the presence of more severe cardiovascular defects in the former. This trend corresponded with the need for cardiovascular support therapy in patients assigned to the DA group, implying that the need for dopamine was determined by the clinical outcomes related to cardiac function. Interestingly,

slight but opposite changes were observed in the dead space parameters VDB and VDE after weaning from CPB. Since VDB reflects ventilated alveoli with absent or insufficient perfusion, minor decreases in this parameter may be attributed to increased bronchial tone and hypocapnia-induced local bronchoconstriction [103]. Conversely, the CPB-induced increase in VDE reflects the expansion of ventilated but poorly perfused or non-perfused alveolar compartments, possibly due to persistent atelectasis after weaning from CPB [132].

Moreover, our findings indicated that deteriorated airway and tissue mechanics, V/Q mismatch, and high VDE after CPB led to impaired oxygenation ability of the lungs and intrapulmonary shunting, determined by the Berggren equation (Fig. 9). The diminished arterial oxygen content secondary to hemodilutional anemia and the declined cardiac output may be responsible for the decrease in SvO_2 after CPB [133], which was distinctly observed in patients who required inotrope therapy.

V.2.2. Effects of dopamine

The compromised airway and tissue mechanics induced by CPB markedly improved with intravenous infusion of dopamine (Fig. 8). This finding aligns with previous demonstrations of dopamine's benefit in relaxing cholinergic [84, 90, 91] or histaminic [85, 90] elevations in bronchial smooth muscle tone and its potential to enhance airway function in patients with chronic obstructive lung disease [71, 86, 87]. The dopamine-induced reductions in the viscoelastic parameters (G and H) of lung tissue may be attributed to improved intrinsic properties of the lung parenchyma through reduced interstitial alveolar edema after CPB [134]. However, this mechanism likely played a minor role within the five-minute window. It is more probable that dopamine facilitated recruitment of atelectatic alveolar compartments after CPB via indirect mechanisms related to significant bronchodilation, which aids in aerating the lung periphery and thereby reduces overall lung tissue stiffness and dissipation [70, 71]. The more pronounced decrease in G compared to H can be explained by reduced heterogeneous constriction of peripheral airways [70, 90]. These changes in forced oscillatory mechanical parameters were also reflected in the R and C values displayed by the ventilator, albeit in a blunted manner, potentially due to the biasing effects of instrumental resistance [113] and the relatively lower sensitivity of C to lung mechanical changes, influenced by increased lung volume at end-inspiration when this parameter is measured [70].

The ability of dopamine to homogenize lung ventilation and improve V/Q matching was further supported by the reduced phase 3 slopes of the time and volumetric capnograms (Fig. 9). The

lack of dopamine effect on VDB suggested that the relative volume of alveolar compartments with high V/Q ratios was not influenced by dopamine. This finding indicated that in these lung zones, improved lung ventilation, as evidenced by enhanced pulmonary mechanics, was accompanied by parallel increases in lung perfusion due to dopamine's positive inotropic effect.

Interestingly, dopamine also decreased VDE, implying that V/Q mismatch might be observed in alveolar regions with low V/Q ratios (intrapulmonary shunting). This apparent contradiction can be explained by dopamine-induced increases in cardiac output, which facilitated CO2 elimination during the study phase while maintaining CO_2 production.

One of the significant findings of this study was the preservation of PaO_2/FiO_2 and Qs/Qt ratios during dopamine administration after weaning from CPB. The maintained gas exchange efficiency of the lungs was consistent with stable physiological dead space and intrapulmonary shunt. The apparent discrepancy between these two parameters reflecting intrapulmonary shunt (VDE and Qs/Qt) can be attributed to the better diffusion coefficient of CO_2 compared to O_2. The lack of changes in these gas exchange parameters is particularly noteworthy given the marked improvements in lung mechanics observed with dopamine.

These data confirmed that dopamine primarily affected the central conducting airways, consistent with previous findings in experimental models of bronchoconstriction [90].

Previous studies have shown no benefit or even worsening of lung oxygenation index and intrapulmonary shunt following dopamine administration in healthy patients [93, 95, 96] and those with sepsis [94]. These findings from earlier reports raise concerns about the potential gas exchange effects of dopamine, especially in patients with underlying lung disorders.

In our study, the increase in cardiac output (Qt) induced by dopamine resulted in proportional increases in shunted intrapulmonary blood flow (Qs), which may explain the lack of change in Qs/Qt. Thus, dopamine did not significantly affect V/Q mismatch after CPB, despite the absolute increase in the shunt fraction.

V.2.3. Study limitations

Certainly, some limitations and technical aspects of our study deserve discussion. One significant limitation was the non-randomized administration of dopamine based on clinical necessity to support the cardiovascular system. This precluded randomization of patients into treatment groups. However, it's important to note that this study design did not introduce bias in most measured outcomes before the intervention period, except for differences observed in Sn3T and VDB, which were clinically expected. This supports the validity of comparisons

between study groups for assessing outcomes related to lung mechanics, ventilation, and gas exchange.

Another technical aspect to consider is the lack of systematic invasive measurement of cardiac output. Instead, evidence for increased cardiac output and improved cardiac function after dopamine infusion was inferred from decreased venoarterial CO_2 content difference and elevated SvO_2 levels [135]. Additionally, the measurement techniques used in our study required general anesthesia and mechanical ventilation, which limited the ability to study intraoperative changes comprehensively. Future studies focusing on the long-term beneficial effects of dopamine post-surgery would be valuable to further understand its impact beyond the immediate recovery phases.

VI. Conclusions

VI.1. Study I.

In conclusion, our analysis of the monthly proportion of cardiac surgeries associated with diabetes, smoking, and elderly age revealed significant seasonal variations, indicating periodic exacerbation of cardiovascular diseases necessitating surgical intervention. Aligning the intensity and timing of care to these seasonal patterns could potentially prevent deterioration in cardiovascular health among diabetes, elderly, and smoking patients. It is recommended that cardiovascular risk factors be systematically assessed at least twice annually in these patient groups. Specifically, assessments should be prioritized during the fall-winter period for patients with diabetes and smoking habits, and during the spring-summer season for elderly individuals.

Effective management of diabetes necessitates more frequent cardiovascular risk assessments than the currently recommended annual evaluation [68, 117], ideally performed at least three times a year with particular attention to monitoring blood pressure and triglyceride levels. Taking into account seasonal trends in risk factors that affect a significant portion of the population could lead to improved patient outcomes and enhance overall healthcare delivery.

VI.2. Study II.

In conclusion, the present study demonstrated dopamine's efficacy in alleviating compromised airway function and ventilation heterogeneities induced by CPB. While these beneficial effects on lung mechanics were observed, they did not translate into improvements in physiologic dead space ventilation or intrapulmonary shunt. Importantly, there was no evidence of detrimental effects on gas exchange abnormalities after weaning from CPB. Therefore, dopamine can be safely recommended in the post-CPB period to enhance cardiac function and mitigate compromised lung function, without adverse consequences on V/Q matching.

Furthermore, our findings suggest the importance of recruitment maneuvers to enhance alveolar ventilation alongside increased cardiac output. This approach is crucial to optimize gas exchange following the mechanical changes induced by weaning from CPB.

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