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Original Article

Dopamine Reverses Lung Function Deterioration After Cardiopulmonary Bypass Without Affecting Gas Exchange

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Objective: To investigate the effects of dopamine on the adverse pulmonary changes after cardiopulmonary bypass.
Design: A prospective, nonrandomized clinical investigation.
Setting: A university hospital.
Participants: One hundred fifty-seven patients who underwent elective cardiac surgery that required cardiopulmonary bypass.
Interventions: Fifty-two patients were administered intravenous infusion of dopamine (3 μg/kg/min) for five minutes after weaning from cardiopulmonary bypass; no intervention was applied in the other 105 patients.
Measurements and Main Results: Measurements were performed under general anesthesia and mechanical ventilation before cardiopulmonary bypass, after cardiopulmonary bypass, and after the intervention. In each protocol stage, forced oscillatory lung impedance was measured to assess airway and tissue mechanical changes. Mainstream capnography was performed to assess ventilation- and/or perfusion-matching by calculating the normalized phase-3 slopes of the time and volumetric capnograms and the physiologic deadspace. Arterial and central venous blood samples were analyzed to characterize lung oxygenation and intrapulmonary shunt. After cardiopulmonary bypass, dopamineinduced marked improvements in airway resistance and tissue damping, with relatively small decreases in lung tissue elastance. These changes were associated with decreases in the normalized phase-3 slopes of the time and volumetric capnograms. The inotrope had no effect on physiologic deadspace, intrapulmonary shunt, or lung oxygenation.
Conclusion: Dopamine reversed the complex detrimental lung mechanical changes induced by cardiopulmonary bypass and alleviated ventilation heterogeneities without affecting the physiologic deadspace or intrapulmonary shunt. Therefore, dopamine has a potential benefit on the gas exchange abnormalities after weaning from cardiopulmonary bypass.

Key Words: inotropes; extracorporeal circulation; respiratory mechanics; capnography; ventilation heterogeneity; intrapulmonary shunt

CARDIAC SURGERY with cardiopulmonary bypass (CPB) initiates a broad spectrum of pathophysiologic changes, including deleterious changes in the respiratory system[1-3] and compromised cardiac pump function after weaning.[4,5] The latter often is treated by the administration of positive inotropic agents,[5] such as dopamine. Dopamine commonly is used in low-to-moderate doses to increase cardiac output, and the

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dose-dependent circulatory effects of this inotrope have been well-characterized.[6,7] In addition to its cardiovascular benefit, dopamine alters lung mechanics by diminishing bronchial smooth muscle tone, which decreases airway resistance,[2,8-15] and has an effect on respiratory tissue viscoelasticity.[2,14,15] However, this improvement of respiratory mechanics by dopamine did not improve, or even worsened, gas exchange. The decreased partial pressure of arterial oxygen (PaO_2) due to dopamine was explained by the increased cardiac output causing an elevated intrapulmonary shunt fraction.[16-20]

The dissociated cardiopulmonary effects of dopamine may raise concerns among clinicians who observe improved lung mechanics but with unchanged or even somewhat worsened gas exchange.[17-20] This seemingly controversial cardiopulmonary effect of dopamine was demonstrated in healthy subjects[17,19,20] and in the presence of sepsis.[18] However, it remains unknown whether this 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. Therefore, the authors here aimed to clarify the effects of dopamine on the respiratory system by comparing its potential to alter respiratory mechanics and V/Q matching in a large cohort of patients who underwent cardiac surgery with CPB.

Methods

Ethics Approval

This single-center prospective nonrandomized clinical trial was approved by the Human Research Ethics Committee, 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 included every item in the CONSORT checklist for a prospective nonrandomized clinical trial.

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), who had an average age of 64 years (range, 32–79 years). Based on the clinical need to support cardiac function by a positive inotrope, the patients were assigned to the dopamine group (DA, n = 52) or the control group (control, n = 105). The administration of dopamine and the allocation of these patients into the DA group was based on a clinical decision algorithm using multimodal monitoring approaches. The main factors in this process involved the patients' history and the clinical parameters during weaning from CPB, such as central venous pressure (>8-10 mmHg), mean arterial pressure (<65 mmHg), central venous oxygen saturation (<70%-75%), and contractility of the left and right ventricles estimated visually in the open chest, or assessed by transesophageal echography. Patients >80 years of age and those with doctor-diagnosed chronic respiratory diseases were excluded. Patients receiving high doses of dopamine, dobutamine, epinephrine, milrinone, or an intra-aortic balloon pump intraoperatively were not included in the study population. Figure 1 shows the flow of participants through the various stages of the trial.

Anesthesia and Surgery

One hour prior to the surgery, all patients were premedicated by 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 a neuromuscular blockade.

Endotracheal intubation was performed using a cuffed tracheal tube that had 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 a volume-control mode with decelerating flow. Ventilation frequency was set to 10-to-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 (F_IO_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 coagulation time maintained >400 seconds. Moderate hypothermia (ie, esophageal temperature of 32°C) routinely was 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 and maintained at this pressure for three seconds to facilitate lung recruitment.

Characterization of Gas Exchange

Arterial and central venous blood samples were used to characterize the gas exchange in 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 (Radiometer ABLTM 505, Copenhagen, Denmark). Blood samples were used to measure the oxygen saturation in the arterial (SaO_2) and venous blood (SvO_2). The lung oxygenation index was calculated as PaO_2/F_IO_2. The intrapulmonary shunt fraction (Qs/Qt) was calculated using the Berggren equation[21]:

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2),$$

where CcO_2, CaO_2, and CvO_2 were the oxygen contents of the pulmonary capillary, artery, and central venous blood, respectively. CcO_2 was calculated according to the alveolar gas

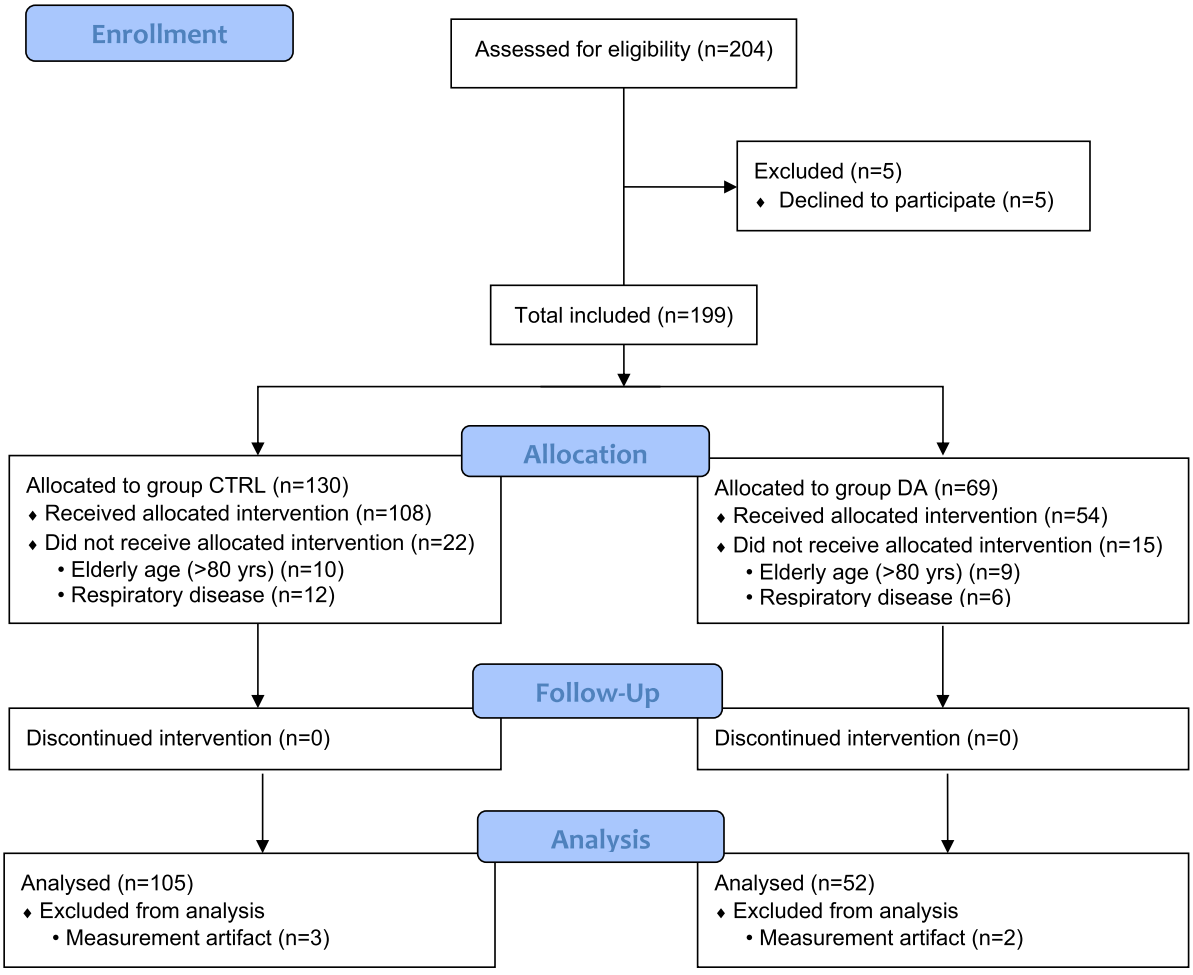

Fig 1. CONSORT flow diagram.

equation, with the assumption that the O_2 saturation of hemoglobin in the pulmonary capillaries was 100%:

$$CcO_2 = 1.34mL/g \times Hb + 0.0031xPAO_2$$

where 1.34 mL/g was the Hüfner's constant, Hb was the hemoglobin concentration in g, 713 mmHg was the total dry gas pressure, and 0.8 was the respiratory exchange ratio, and alveolar oxygen tension (PAO_2) was derived from the alveolar gas equation:

$$PAO_2 = 713mmHgxF_IO_2 - PaCO_2/0.8$$

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.[1,22] Volumetric capnograms were constructed from the CO_2 and integrated flow signals. Time capnograms in the time domain, which are routinely displayed in clinical practice, were analyzed.

The phase-3 slopes of the time ($S3_T$) and volumetric ($S3_V$) capnograms were determined by fitting a linear regression line to the last 60% of phase 3.[23-25] To take into account the absolute concentration of CO_2 in the expired gas, both $S3_T$ and $S3_V$ were normalized ($Sn3_T$ and $Sn3_V$, respectively) by dividing each slope by the average value of the corresponding end-tidal CO_2 concentration in the mixed expired gas.[26-28] In addition, deadspace fraction was calculated from the volumetric capnograms. The physiologic deadspace fraction according to Bohr (VD_B), which reflects the alveolar volume with decreased or no perfusion, was calculated from the capnograms as follows[29]:

$$VD_B/V_T = (P_{ACO_2} - P_{E\bar{C}O_2})/P_{ACO_2},$$

where P_{ACO2} was the mean alveolar partial pressure of CO_2 in the midpoint of phase 3 in the capnograms.[30,31] $P_{\bar{E}CO2}$ was the partial pressure of mixed expired CO2 and was obtained by calculating the area under the volumetric capnogram curves by integration and dividing the resulting values by V_T.

The physiologic deadspace calculated by Enghoff's approach (VD_E) provides additional information on V/Q

mismatch. Therefore, in addition to the V_{DB}, the intrapulmonary shunt (ie, alveolar volume with decreased or absent ventilation but maintained perfusion) was incorporated. VD_E was calculated as follows[32]:

$$VD_E/V_T = (P_{aCO_2} - P_{ECO_2})/P_{aCO_2}$$

Measurement of Airway and Lung Tissue Mechanics by Forced Oscillations

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.[1,2] 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 connected 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 seconds) end-expiratory apneic pauses from mechanical ventilation. The forcing signal comprised 15 multiple integer components that had 0.4 Hz as fundamental frequency, 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 airway opening pressure (Pao). ZL was computed from the power spectra of Pao and V'; the ensemble average was determined under each condition. The mean ZL data were fitted by a well-validated four-parameter model,[33] which contained frequency-independent airway resistance (Raw) and inertance (Iaw) and a constant-phase tissue compartment that was characterized by the coefficients of damping (G) and elastance (H); this way, the difference between the measured and modeled impedance values was minimal. Raw represented the flow resistance of the bronchial tree, whereas Iaw was related with the mass of the gas in the airways; these parameters, Raw and Iaw, were corrected to the instrumental resistance and inertance of the measurement apparatuses, including the endotracheal tube.[1,2,34] The tissue parameters characterized the resistive (G) and elastic properties of the lung parenchyma (H).

Measurement Protocol

Upon stabilization of the hemodynamic and respiratory mechanical conditions after midline sternotomy, measurements were performed five minutes before starting CPB (pre-CPB). The 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 group DA received an intravenous infusion of dopamine, 3 μg/kg/min. Five minutes after initiating the dopamine infusion, the third data collection step was taken in the same manner as detailed earlier (ie, intervention: INT). The same timing and data collection procedures were followed for patients in whom the administration of any inotrope or other vasoactive or bronchoactive drugs was not needed (control group).

Statistical Analyses

Scatters in measured variables were expressed as a 95% confidence interval of the mean. Normality of the data was checked with the Kolgomorov-Smirnov test with Lilliefors correction. Two-way repeated measures analysis of variance, with the inclusion of an interaction term, was used for all of the 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 SigmaPlot software package (Version 14, Systat Software, Inc., Chicago, IL). All reported p values were two-sided.

Results

Sex, age, height, body weight, and the parameters related with the surgery types did not significantly differ between the protocol groups (Table 1).

Figure 2 demonstrates the airway and lung tissue mechanical parameters at the different protocol stages in both study groups. CPBinduced 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 the R and C on the ventilator display.

The normalized shape factors and deadspace parameters obtained by time and volumetric capnography are summarized in Figure 3. The elevations in $Sn3_T$ and $Sn3_V$ after CPB were associated with decreases in VD_B in both groups ($p < 0.001$ for both), whereas VD_E was elevated only in group DA ($p <$

Table 1
Demographic, Anthropometric, and Clinical Characteristics of the Patients

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

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.

0.005). The DA group had significantly decreased $Sn3_T$, $Sn3_V$, and VD_E ($p < 0.01$ for all) but no detectable change in VD_B. In the control group, the corresponding changes in any of those parameters did not reach statistical significance in the intervention period (post-CPB versus INT).

The changes in the parameters associated with oxygenation and intrapulmonary shunt are demonstrated in Figure 4. In both groups, CPB significantly decreased the PaO_2/F_IO_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/F_IO_2 and Qs/Qt, but there was a significant increase in SvO_2 and a significant decrease in $PvCO_2-PaCO_2$ ($p < 0.001$ for both).

Discussion

In this large cohort of patients who underwent cardiac surgery with CPB, the study authors observed that the ability of dopamine to improve airway and lung tissue mechanics was associated with its benefit on V/Q matching. The importance of the study stemmed from the fact that previous studies reported that the beneficial effects of dopamine on airway function may be associated with its potentially deleterious consequences on V/Q matching. Forced oscillatory measurements demonstrated the ability of dopamine to reverse the detrimental lung function changes that were induced by extracorporeal circulation. In addition, capnography and blood gas measurements revealed that these mechanical changes were associated with improvements in V/Q matching and deadspace ventilation without any detrimental consequences on lung oxygenation or intrapulmonary shunt.

Effects of CPB

The systemic inflammatory response after CPB leads to pathophysiologic changes, which range from mild organ dysfunction to multisystem organ failure, with the lungs being one of the most commonly affected organs.[35,36] Accordingly, prominent bronchoconstriction after CPB was observed. This airway pathology was associated with moderate but significant deteriorations in the viscoelastic properties of the lung tissue (Fig 2), which can be attributed to intrinsic alteration in the lung tissue properties and/or atelectasis development. The forced oscillatory airway and tissue changes were more sensitive, compared with 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 the airway resistance.[34] Although the current results on the effects of CPB on lung mechanics were in accordance with those reported previously,[1-3] 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.[35-37] Deterioration in lung tissue viscoelasticity after CPB can be a consequence of intrinsic changes in the dissipation and elastic properties of the pulmonary parenchyma secondary to interstitial edema formation,[38] in addition to persistent alveolar derecruitment; these lead to heterogeneous loss of ventilated lung volume.[39]

The association of the 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 3). Notably, the $Sn3_T$ value tended to be greater in group DA than in the control group; this result 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 who were assigned to group DA, thereby 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 deadspace parameters VD_B and VD_E after weaning from CPB. Because VD_B 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.[22] Conversely, the CPB-induced increase in VD_E reflects expansion of ventilated but poorly perfused or nonperfused alveolar compartments, which may be a consequence of persistent atelectasis after weaning from CPB.[39]

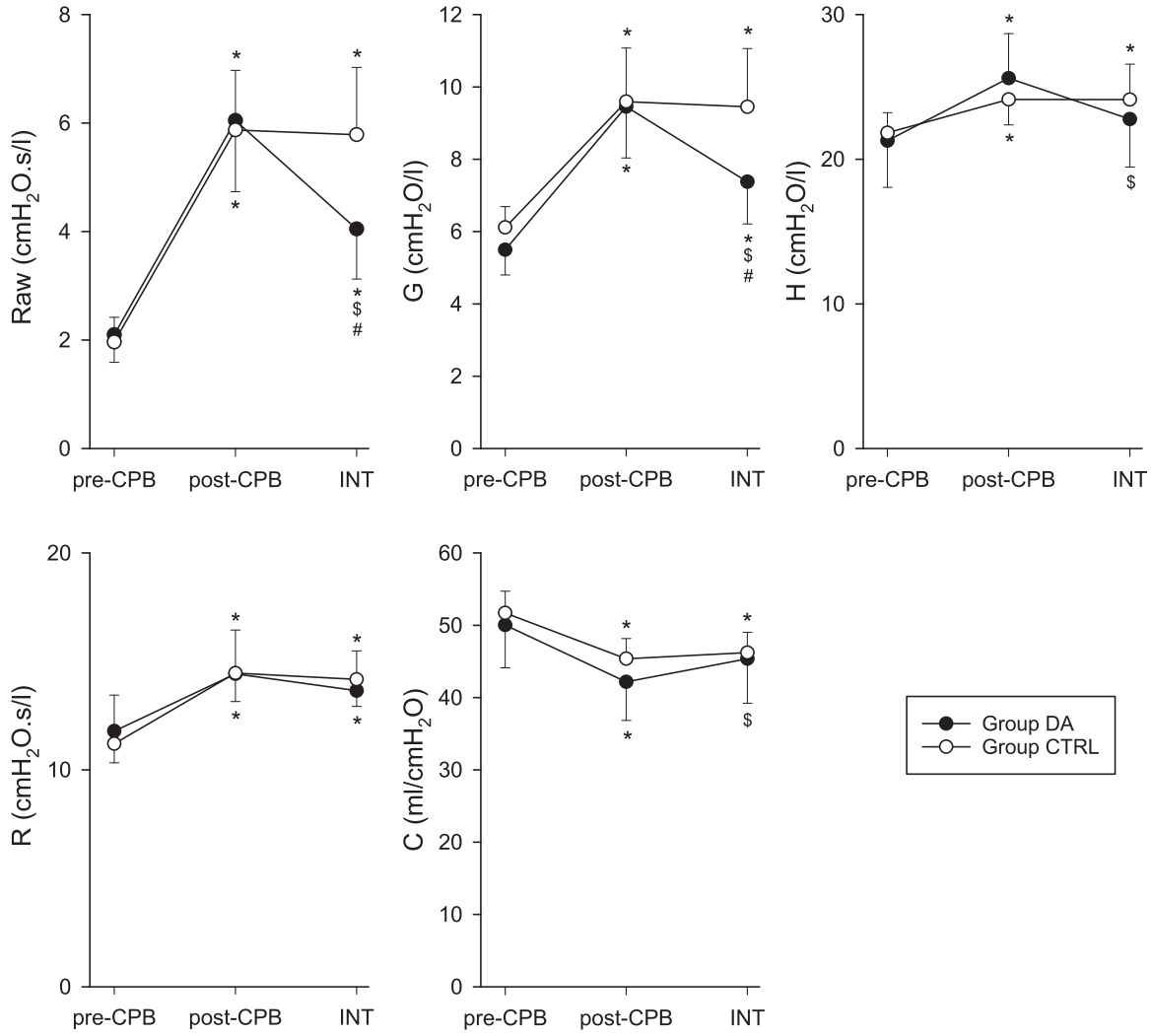

Fig 2. Mean (symbols) with 95% confidence interval (error bars) of the forced oscillatory airway resistance (Raw) and lung tissue damping (G) and elastance (H) in patients treated with 3 μg/kg/min of dopamine (DA group, n = 52) and in patients who did not receive the inotrope (control group, n = 105); *p < 0.05 vs. 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.

Moreover, the authors' findings indicated that deteriorated airway and tissue mechanics, V/Q mismatch, and high VD_E after CPB led to impaired oxygenation ability of the lungs and intrapulmonary shunting, which was determined by the Berggren equation (Fig 4). 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,[40] which was distinctly observed in patients who required inotrope therapy.

Effects of Dopamine

The compromised airway and tissue mechanics induced by CPB improved markedly by the intravenous infusion of dopamine (Fig 2). This finding was in accordance with the previously demonstrated benefit of dopamine in relaxing the cholinergic[8,14,15] or histaminic[9,14] elevations in bronchial smooth muscle tone and its potential to improve airway function in patients with chronic obstructive lung disease.[2,10,11] The dopamine-induced drops in the viscoelastic parameters (ie, G and H) of the lung tissue may be attributed to the improvement of the intrinsic properties of the lung parenchyma through reduction of the interstitial alveolar edema after CPB.[41] However, this mechanism was unlikely to play a major role in the five-minute window. It seemed more probable that dopamine enabled the recruitment of some atelectatic alveolar compartments after CPB via indirect mechanisms related to the marked bronchodilation that facilitates aeration of the lung periphery, thereby reducing overall lung tissue stiffness and dissipation.[1,2] The more pronounced drops in G than in H can be explained by the decreased heterogeneous constriction of the peripheral airways.[1,14] These changes in the forced oscillatory mechanical parameters likewise were manifested in the R and C values displayed by the ventilator, although in a blunted manner; this may be secondary to the biasing effects of the instrumental resistance[34] and the

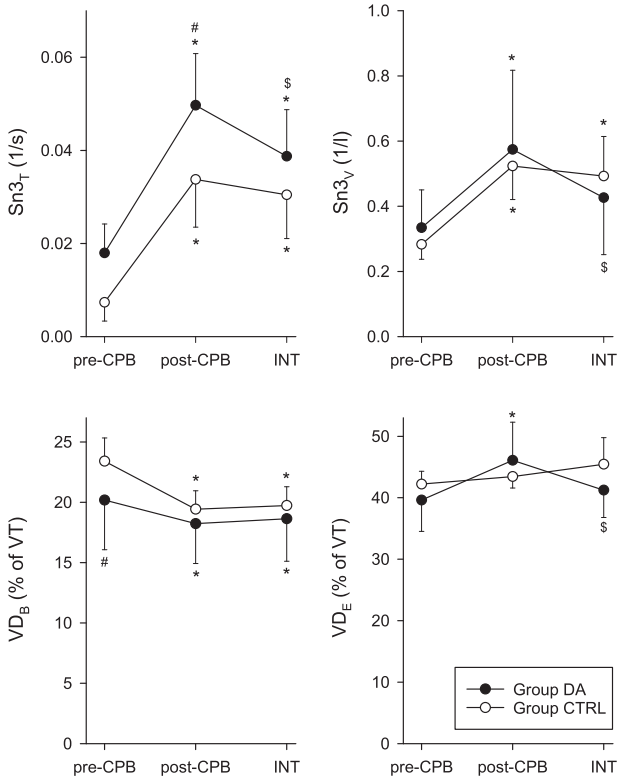

Fig 3. Mean (symbols) with 95% confidence interval (error bars) of the normalized phase-3 slope of time ($Sn3_T$) and volumetric capnograms ($Sn3_V$) and the ventilation deadspace fractions according to Bohr (VD_B) and Enghoff (VD_E) in patients treated with 3 μg/kg/min of dopamine (DA group, n = 52) 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.

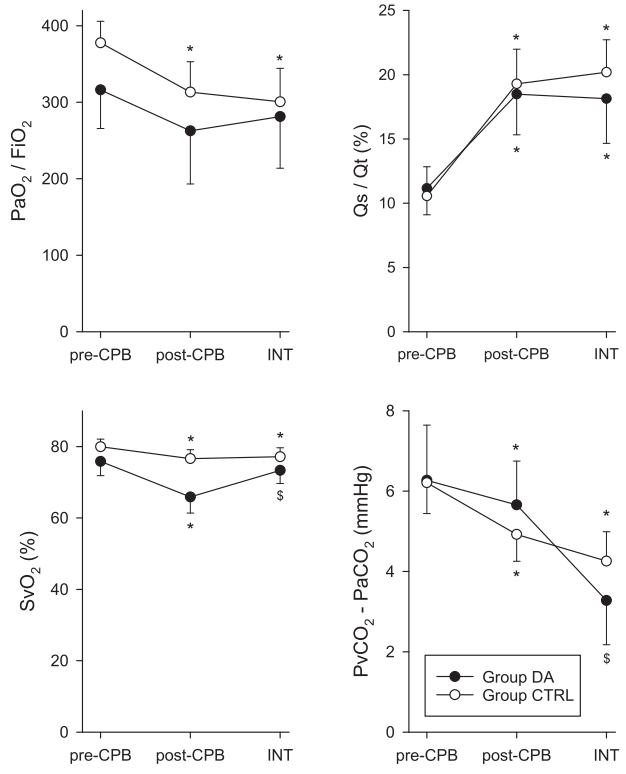

Fig 4. Mean (symbols) with 95% confidence interval (error bars) of the lung oxygenation index (PaO_2/F_IO_2), intrapulmonary shunt (Qs/Qt), venous oxygen saturation (SvO_2), and venoarterial carbon dioxide difference ($PvCO_2$-$PaCO_2$) in patients treated with 3 μg/kg/min of dopamine (DA group, n = 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.

relatively low sensitivity of C to lung mechanical changes, due to the increased lung volume at end-inspiration when this parameter is measured.[1]

The ability of dopamine to homogenize lung ventilation and improve V/Q matching was further evidenced by the diminished phase-3 slopes of the time and volumetric capnograms (Fig 3). The absence of dopamine effect on the VD_B implied that the relative volume of alveolar compartments with high V/Q ratio was not affected by dopamine. This finding indicated that in these lung zones, enhanced lung ventilation, as demonstrated by the improved pulmonary mechanics, was associated with parallel increases in lung perfusion because of the positive inotropic effect of dopamine. Interestingly, dopamine decreased VD_E, suggesting that V/Q mismatch may be detected when alveolar regions with low V/Q ratio (intrapulmonary shunting) are taken into account. This apparent controversy can be explained by the dopamine-induced increase in cardiac output, which facilitated elimination of CO_2 during this short phase of the study while its production was maintained.

One of the most prominent findings of the present study was preservation of the PaO_2/F_IO_2 and Qs/Qt during dopamine administration after weaning from CPB. The maintained gas exchange ability of the lungs was in accordance with the constant physiologic deadspace and intrapulmonary shunt. These seemingly contradicting findings between the two parameters that reflect intrapulmonary shunt (ie, VD_E and Qs/Qt) can be explained by the better diffusion coefficient of CO_2 than of O_2. The absence of changes in these gas exchange parameters is of particular interest in the context of marked improvements in lung mechanics. Taken together, these data confirmed that dopamine had a bronchial effect, which was mainly on the central conducting airways, as demonstrated previously in an experimental model of bronchoconstriction.[14] Previous findings demonstrated a lack of benefit or even worsened lung oxygenation index and intrapulmonary shunt after dopamine administration in healthy patients[17,19,20] and in those with sepsis.[18] These results from earlier reports may raise concerns about the gas exchange benefit of dopamine, particularly in patients with lung disorders. In the present study, the authors found that the increase in cardiac output (Qt) caused by dopamine led to proportional elevations in shunted intrapulmonary blood flow (Qs); this may explain the absence of change in the Qs/Qt. Accordingly, dopamine had no effect on the V/Q mismatch after CPB, despite the increased absolute value of the shunt fraction.

Study Limitations

Some limitations and technical aspects of this study warrant discussion. Because the administration of dopamine was based

on the clinical need to support the cardiovascular system, randomization of the patients into groups was not possible. However, this study design did not cause bias in most of the measured outcomes before the intervention period, with differences observed only in the $Sn3_T$ and VD_B, in agreement with the clinical symptoms. This fact confirmed the validity of the comparisons between the study groups for the assessment of outcomes on lung mechanics, ventilation, and gas exchange. A further technical aspect of the study was the lack of systematic invasive measurement of the cardiac output. Nevertheless, the decreased venoarterial CO_2 content difference and the elevated SvO_2 provided evidence for the increased cardiac output and improved cardiac function after dopamine infusion.[42] Because the measurement techniques applied in the present study required general anesthesia and mechanical ventilation, studying the intraoperative changes was the focus. Further studies are required to identify the long-term beneficial effects of dopamine after surgery.

Summary and Conclusions

In conclusion, the present study demonstrated the ability of dopamine to alleviate compromised airway function and ventilation heterogeneities that were triggered by CPB. Although these favorable effects of dopamine on lung mechanics were not reflected in the physiologic deadspace ventilation or intrapulmonary shunt, there was no evidence of any disadvantage on the gas exchange abnormalities after weaning from CPB. Therefore, this inotrope can be safely recommended in the post-CPB period to improve cardiac function and to mitigate the compromised lung function, without the risk for disadvantageous consequences on V/Q matching. Moreover, the findings here implied the need for recruitment maneuvers to increase alveolar ventilation, along with the increased cardiac output, in order to allow gas exchange to improve with the lung mechanical changes after weaning from CPB.

Conflict of Interest

None.

References

1 Balogh AL, Petak F, Fodor GH, et al. Sevoflurane relieves lung function deterioration after cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2017;31:2017–26.
2 Babik B, Asztalos T, Petak F, et al. Changes in respiratory mechanics during cardiac surgery. Anesth Analg 2003;96:1280–7.
3 Imura H, Caputo M, Lim K, et al. Pulmonary injury after cardiopulmonary bypass: Beneficial effects of low-frequency mechanical ventilation. J Thorac Cardiovasc Surg 2009;137:1530–7.
4 Monaco F, Di Prima AL, Kim JH, et al. Management of challenging cardiopulmonary bypass separation. J Cardiothorac Vasc Anesth 2020;34:1622–35.
5 Lomivorotov VV, Guvakov D, Belletti A, et al. Current practice of calcium use during cardiopulmonary bypass weaning: Results of an international survey. J Cardiothorac Vasc Anesth 2020;34:2111–5.
6 Petersen JW, Felker GM. Inotropes in the management of acute heart failure. Crit Care Med 2008;36:S106–11.
7 Farmakis D, Agostoni P, Baholli L, et al. A pragmatic approach to the use of inotropes for the management of acute and advanced heart failure: An expert panel consensus. Int J Cardiol 2019;297:83–90.
8 Advenier C, Saint-Aubin A, Mallard B, et al. Bronchopulmonary effects of dopamine in the guinea-pig. Arch Int Pharmacodyn Ther 1980;243:261–74.
9 Michoud MC, Amyot R, Jeanneret-Grosjean A. Dopamine effect on bronchomotor tone in vivo. Am Rev Respir Dis 1984;130:755–8.
10 Cabezas GA, Israili ZH, Velasco M. The actions of dopamine on the airways. Am J Ther 2003;10:477–86.
11 Cabezas GA, Lezama Y, Vidal A, et al. Inhaled dopamine induces bronchodilatation in patients with bronchial asthma. Int J Clin Pharmacol Ther 1999;37:510–3.
12 Mizuta K, Zhang Y, Xu D, et al. The dopamine D(2) receptor is expressed and sensitizes adenylyl cyclase activity in airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 2012;302:L316–24.
13 Mizuta K, Zhang Y, Xu D, et al. The dopamine D1 receptor is expressed and facilitates relaxation in airway smooth muscle. Respir Res 2013;14:89.
14 Fodor GH, Balogh AL, Sudy R, et al. Dopamine ameliorates bronchoconstriction induced by histaminergic and cholinergic pathways in rabbits. Respir Physiol Neurobiol 2019;259:156–61.
15 Fodor GH, Bayat S, Babik B, et al. Reversing cholinergic bronchoconstriction by common inotropic agents: A randomized experimental trial on isolated perfused rat lungs. Anesth Analg 2019;129:745–52.
16 Bryan TL, van Diepen S, Bhutani M, et al. The effects of dobutamine and dopamine on intrapulmonary shunt and gas exchange in healthy humans. J Appl Physiol (1985) 2012;113:541–8.
17 Russell WJ, James MF. The effects on arterial haemoglobin oxygen saturation and on shunt of increasing cardiac output with dopamine or dobutamine during one-lung ventilation. Anaesth Intensive Care 2004;32:644–8.
18 Jardin F, Gurdjian F, Desfonds P, et al. Effect of dopamine on intrapulmonary shunt fraction and oxygen transport in severe sepsis with circulatory and respiratory failure. Crit Care Med 1979;7:273–7.
19 Rennotte MT, Reynaert M, Clerbaux T, et al. Effects of 2 inotropic drugs, dopamine and dobutamine, on pulmonary gas exchange in artificially ventilated patients. Intensive Care Med 1989;15:160–5.
20 Rapin M, Lemaire F, Regnier B, et al. Increase of intrapulmonary shunting induced by dopamine. Proc R Soc Med 1977;70 Suppl 2:71–5.
21 Berggren S. The oxygen deficit of arterial blood caused by non-ventilating parts of the lung. Acta Physiol Scand 1942;4.
22 Csorba Z, Petak F, Nevery K, et al. Capnographic parameters in ventilated patients: Correspondence with airway and lung tissue mechanics. Anesth Analg 2016;122:1412–20.
23 Babik B, Csorba Z, Czovek D, et al. Effects of respiratory mechanics on the capnogram phases: Importance of dynamic compliance of the respiratory system. Crit Care 2012;16:R177.
24 Krauss B, Deykin A, Lam A, et al. Capnogram shape in obstructive lung disease. Anesth Analg 2005;100:884–8.
25 Blanch L, Lucangelo U, Lopez-Aguilar J, et al. Volumetric capnography in patients with acute lung injury: Effects of positive end-expiratory pressure. Eur Respir J 1999;13:1014–48.
26 Ream RS, Schreiner MS, Neff JD, et al. Volumetric capnography in children. Influence of growth on the alveolar plateau slope. Anesthesiology 1995;82:64–73.
27 Tusman G, Areta M, Climente C, et al. Effect of pulmonary perfusion on the slopes of single-breath test of CO2. J Appl Physiol 2005;99:650–5.
28 Tsoukias NM, Tannous Z, Wilson AF, et al. Single-exhalation profiles of NO and CO2 in humans: Effect of dynamically changing flow rate. J Appl Physiol 1998;85:642–52.
29 Bohr C. Über die lungenatmung. Skan Arch Physiol 1891;53:236–8.
30 Tusman G, Sipmann FS, Bohm SH. Rationale of dead space measurement by volumetric capnography. Anesth Analg 2012;114:866–74.
31 Tusman G, Sipmann FS, Borges JB, et al. Validation of Bohr dead space measured by volumetric capnography. Intensive Care Med 2011;37:870–4.
32 Enghoff H. Volumen inefficax. Uppsala Laekareforen Forh 1938;44:191–218.
33 Hantos Z, Daroczy B, Suki B, et al. Input impedance and peripheral inhomogeneity of dog lungs. J Appl Physiol (1985) 1992;72:168–78.

34 Babik B, Petak F, Asztalos T, et al. Components of respiratory resistance monitored in mechanically ventilated patients. Eur Respir J 2002;20:1538–44.
35 Gao M, Xie B, Gu C, et al. Targeting the proinflammatory cytokine tumor necrosis factor-alpha to alleviate cardiopulmonary bypass-induced lung injury (review). Mol Med Rep 2015;11:2373–8.
36 He G, Li Q, Li W, et al. Effect of ulinastatin on interleukins and pulmonary function in bypass patients: A meta-analysis of randomized controlled trials. Herz 2020;45:335–46.
37 Wojtecka-Lukasik E, Karolczak MA, Maslinska D, et al. Histamine and oxygen radicals of blood in the course of cardiopulmonary bypass (CPB). Inflamm Res 2006;55 Suppl 1:S75–6.
38 Conti VR. Pulmonary injury after cardiopulmonary bypass. Chest 2001;119:2–4.
39 Verheij J, van Lingen A, Raijmakers PG, et al. Pulmonary abnormalities after cardiac surgery are better explained by atelectasis than by increased permeability oedema. Acta Anaesthesiol Scand 2005;49:1302–10.
40 Habib RH, Zacharias A, Schwann TA, et al. Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: Implications on operative outcome. Crit Care Med 2005;33:1749–56.
41 Vohra PK, Hoeppner LH, Sagar G, et al. Dopamine inhibits pulmonary edema through the VEGF-VEGFR2 axis in a murine model of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2012;302:L185–92.
42 Laszlo G. Respiratory measurements of cardiac output: from elegant idea to useful test. J Appl Physiol (1985) 2004;96:428–37.