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Characterization of the Pulmonary Circulation According to Hemodynamic Changes by Computed Tomography

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Increased or decreased pulmonary blood flow (PBF) and an increased pulmonary vascular resistance (PVR), represent common and important change in pulmonary hemodynamics. In this study, we constructed 3 hemodynamic models in 5 dogs, that is, an increased and a decreased PBF model, and an increased PVR model. A CT perfusion scan was performed in each hemodynamic model. Perfusion parameters including blood flow (BF), blood volume (BV), mean transit time (MTT), and maximal slope (MS) were calculated automatically by specialized software and analyzed for changes according to hemodynamic status. In terms of the normal state, blood flow was affected by gravity and dependent area showed higher BF and BV and lower MS and MTT than the non-dependent area. The decreased PBF model showed a significant increase in BF and MS (p=0.046, 0.005) but no significant change in BV ($p>$ 0.05), and a slight elongation of MTT ($p>0.05$) versus the normal state. The increased PBF model showed a slightly increased BV and a slightly decreased MTT ($p>0.05$). The increased PVR model showed significant reduction in BF, BV, and MS ($p<0.000$, 0.007, 0.000) and a slight increase in MTT, but without statistical significance ($p>0.05$). However, it was noticeable that the distribution of MTT with respect to gravity in the normal lung was completely reversed in the increased PVR model. In conclusion, based on our understanding of perfusion characteristic in normal state, abnormal regional hemodynamic changes in the lung can be detected and evaluated. Predicting changes in pulmonary vascular resistance should be possible by a thorough analysis of CT perfusion parameters.

Key Words: Pulmonary imaging, computed tomography, pulmonary regional perfusion, physiologic imaging, pulmonary microcirculation (medicus indecus)

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INTRODUCTION

Hemodynamic parameters including pulmonary resistance are the most important considerations when deciding upon the modality of treatment or when anticipating prognosis in congenital heart disease. However, these parameters are obtained clinically by invasive measurements involving cardiac catheterization and by indirect calculations based on these measurements. In addition, these parameters represent only the summation of pulmonary regional hemodynamics. Thus, it would be useful to non-invasively evaluate regional pulmonary hemodynamics. The most common and important change in pulmonary hemodynamics in congenital heart disease is represented by an increased or a decreased pulmonary blood flow (PBF) and an increased pulmonary vascular resistance (PVR). Thin-section computed tomography (CT) can visualize vessels with up to 300μm in diameter, and the background density of the lung parenchyma represents a vascular density created by vessels with smaller diameters than 300μm. However, this background density can be easily affected by the volume of air, interstitial thickness, and body fluid.[1-7] Microfocal angiography is an accurate method for evaluating regional blood flow, but is not applicable in clinical practice.[8,9] Digitalized angiography is also an invasive method.[10,11] Of the

various methods used to evaluate pulmonary blood flow, dynamic CT scanning with a bolus injection of iodine contrast material is expected to be a effective method, because it has high resolution and a short scan time.[12-17] Wolfkiel, et al. studied pulmonary perfusion using electron beam CT and utilized a single compartment model for this purpose. This is the same method that was applied in a perfusion study of the myocardium.[12] Clough et al. proved that mean transit time, a important perfusion parameter, could be accurately calculated using a single compartment model and indicator dilution theory with CT.[18] However, no study has been conducted to determine how these perfusion parameters, assessed by perfusion study with CT, are related with clinically important hemodynamic changes, including decreased and increased PBF, and increased PVR.

In this animal experiment, a CT perfusion scan was performed in three different hemodynamic models, that is, in an increased and a decreased PBF model, and in an increased PVR model. Perfusion parameters, which included blood flow (BF), blood volume (BV), mean transit time (MTT), and maximal slope (MS) were analyzed with regard to the manner in which they changed with respect to hemodynamic changes, and whether regional hemodynamic changes can be evaluated. Using a noninvasive technique, based on CT perfusion parameters, we evaluated whether each hemodynamic state could be differentiated.

MATERIALS AND METHODS

Hemodynamic model

Three hemodynamic models were constructed for the experiment. To create an increased and a decreased pulmonary blood flow (PBF) model, we partially occluded the left pulmonary artery with a balloon-tipped catheter, and used the lung with this occluded pulmonary artery as a decreased PBF model and the contralateral lung as an increased PBF model. To make an increased pulmonary vascular resistance (PVR) model, 50 μm of gelfoam particles (Gelfoam; absorbable gelatin powder, The Upjohn Company, Kalamazoo, Michigan 49001, USA), which have the smallest particle size of embolic materials in clinical practice, were infused into the main pulmonary artery to occlude the pulmonary microcirculation.

Animal preparation

Five adult dogs (20 - 25kg) were included in this study. General anesthesia was performed with 50 mg/kg sodium pentobarbital and 2 mg/kg of succinyl choline; animals were maintained by mechanical ventilation. Four catheters were inserted into each dog (Fig. 1). First, a 5F Swan-Ganz catheter (Edward's Swan-Ganz true size pediatric thermodilution catheter; Baxter Healthcare Corporation, Edwards Critical-Care Division Irvine, CA, USA) was inserted through the right jugular vein into the right pulmonary artery to measure right pulmonary arterial pressure, pulmonary arterial wedge pressure, and the cardiac output using the thermodilution technique. Second, a 7F multi-hole catheter (7FR BERMAN ARROW, Arrow International, Inc. Reading, PA, USA) was inserted by right femoral venotomy into the main pulmonary artery for the bolus injection of contrast material, for the infusion of gelfoam particles to create the increased PVR model, and to measure pressure in the main pulmonary artery. Third, a 7F end-hole balloon

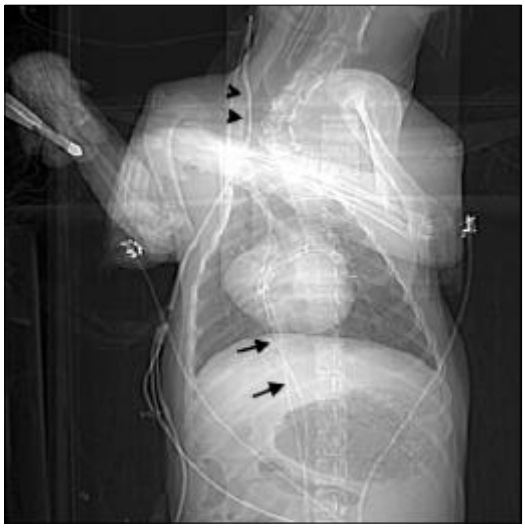

Fig. 1. Four catheters inserted in each dog. A Swan-Ganz catheter (arrowhead) and two 7F-catheters (arrows) are shown. A 5F catheter inserted into a femoral artery is not shown.

catheter (7FR BERMAN ARROW BALLOON CAP 0.75 cc) was inserted by left femoral venotomy into the left pulmonary artery to measure left pulmonary arterial pressure, and to occlude the left pulmonary artery to create the decreased PBF model. Finally, a 5F catheter was inserted into the right femoral artery for monitoring systemic blood pressure. Heparin sodium (100 units/kg) was intravenously infused to prevent thrombosis before catheter insertion.

CT protocol: perfusion scan

A perfusion CT scan was performed after the successful insertion of all catheters. The time interval between animal preparation and the first CT scan, including the time needed to transfer an animal to the CT room and CT preparation time, including the setting up of monitoring devices and the ventilator was about 30 to 40 minutes.

CT perfusion scans (Hispeed, GE medical systems, Milwaukee, Wisconsin, USA) in the supine position, were performed while the ventilator was off at functional residual volume. Bolus injection time (0.5 ml/kg, 10 ml/second) of the ioxehol contrast material (Omnipaque 300; Nycomed, Oslo, Norway) was about 1 second. Scans were started 2 seconds before the injection of contrast material to obtain base images. A total of 22 images were obtained at one second intervals at a single location. Scans were performed at 4 locations, i.e., at the aortic arch level, at the carina, midway between the carina and diaphragm, and 2 cm above the diaphragm in each model in each dog. The scan interval was more than 5 minutes to allow for contrast material wash out. CT scans was repeated consecutively in the order; increased and decreased PBF, in the normal state, and finally in the increased PVR model. CT scans in the increased and decreased PBF models were started about 30 - 40 minutes after pulmonary artery balloon-occlusion. CT scanning in the normal state was started about 20 minutes after releasing the balloon, to allow for the restoration of the normal physiology, which was monitored using heart rate and pulmonary and systemic arterial pressures versus baseline values measured before occlusion. CT scans in the increased PVR model were started when the pulmonary arterial pressure reached 20 mmHg after gelfoam infusion.

The EKG and pulmonary arterial and systemic arterial pressures were constantly monitored and recorded immediately after each CT scan in each model. Cardiac output and pulmonary wedge pressure were measured twice before and after the CT scanning of each model. Mean values of these invasively measured parameters in each hemodynamic model were used for comparative purposes versus the parameters calculated from CT data and for calculating pulmonary vascular resistance (PVR).

Analysis

CT perfusion analysis software in Advanced Workstation 4.0 (GE Medical Systems, Milwaukee, Wis) was used throughout. A region of interest (ROI) was drawn for whole lung (Fig. 2) and multiple ROIs were drawn for the dependent 1/3, the non-dependent 1/3, and the intermediate 1/3 areas with respect to gravity (Fig. 3). ROIs were drawn carefully to exclude vessels of diameter >1 mm, and atelectasis or consolidation. The time-density curve for each ROI was obtained automatically using the above software (Fig. 4). The characteristics of each time-density curve were analyzed. Various perfusion parameters were calculated from the time-density curve by Gamma variate fitting, these included blood flow (BF; ml/

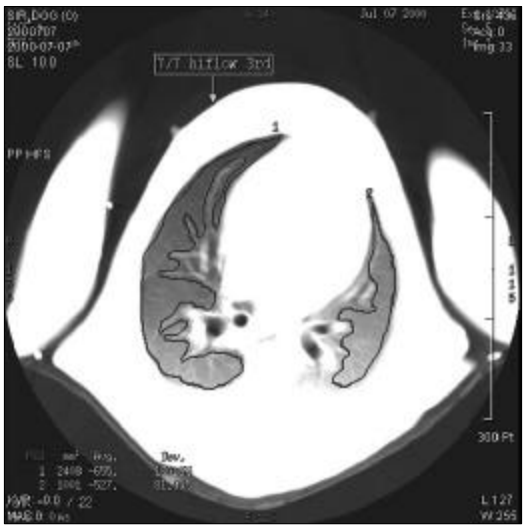

Fig. 2. Drawing the region of interest on each lung. The region of interest is carefully drawn to exclude vessels with a diameter of more than 1 mm.

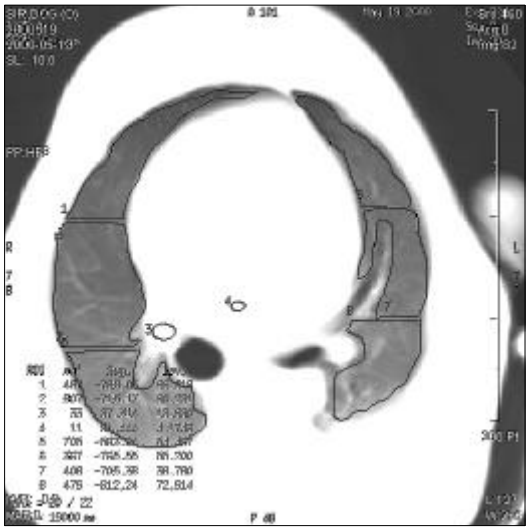

Fig. 3. Drawing the region of interest. Region of interest is drawn by dividing the lung into three zones of equal height with respect to gravity in each lung.

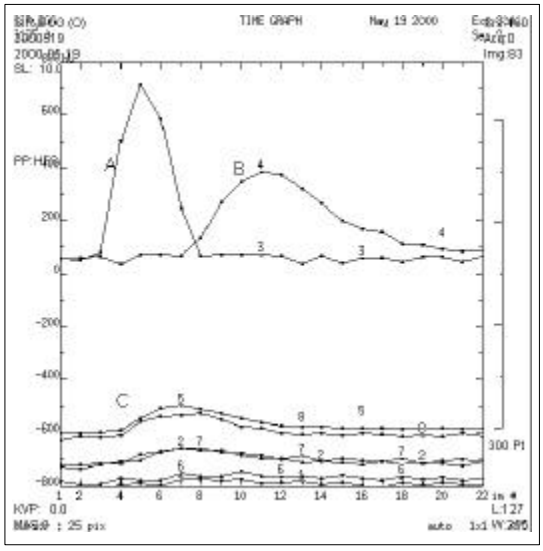

Fig. 4. Time-density curve. A typical time-density curve showing arterial input (A), a venous output curve (B), and curves of the regional lung parenchyma with respect to gravity (C).

min/100g), blood volume (BV; ml/100g), mean transit time (MTT; second), and maximal slope (MS; HU/second).[19] Blood volume was calculated by integrating the time-density curve. Mean transit time was defined at the width at a half of the maximal density shown by the time-density curve. Blood flow was defined as blood volume divided by the mean transit time. These parameters were calculated for the different regions of interest in the lung, and changes in these lung perfusion parameters were assessed with respect to gravity. The paired t-test was used to estimate differences in perfusion parameters in the whole lung with respect to gravity between in the normal hemodynamic state and in the abnormal hemodynamic states. Correlations between CT perfusion parameters and invasively measured hemodynamic parameters were evaluated using the Pearson correlation test.

RESULTS

Normal hemodynamic status

In the 10 lungs of 5 dogs, pulmonary blood flow in the normal hemodynamic state increased toward the dependent area and the dependent area revealed higher BF and BV and lower MS and MTT than non-dependent area (Fig. 5, 6, and 7).

Decreased pulmonary blood flow model

In 5 left lungs with a partially occluded proximal pulmonary artery, BF and MS in the decreased PBF model were significantly lower than their baseline values (89.52 ± 33.05 ml/min/100g < 103.61 ± 15.61 ml/min/100g, p=0.046) (39.14 ± 14.59 HU/second < 50.46 ± 21.87 HU/second, p=0.005). However, BV (19.50 ± 11.59 ml/100g) in the decreased PBF model showed no change (19.54 ± 7.54 ml/100g) (p=0.978), whereas MTT increased slightly, but this was not statistically significant (8.08 ± 3.37 seconds > 6.70 ± 2.46 seconds, p=0.101).

Increased pulmonary blood flow model

In 5 right lungs contralateral to the left lungs with an occluded proximal pulmonary artery, BF, BV, and MS showed slight increase versus baseline (97.32 ± 19.40 ml/min/100g > 94.63 ± 15.07 ml/min/100g, p=0.352) (17.64 ± 7.23 ml/100g > 15.63 ± 7.54 ml/100g, p=0.125) (42.53 ± 13.07 HU/second > 41.43 ± 12.26 HU/second, p=0.422), and MTT showed a tendency to decrease (6.06 ± 2.33 seconds < 6.70 ± 2.331 seconds, p=0.220).

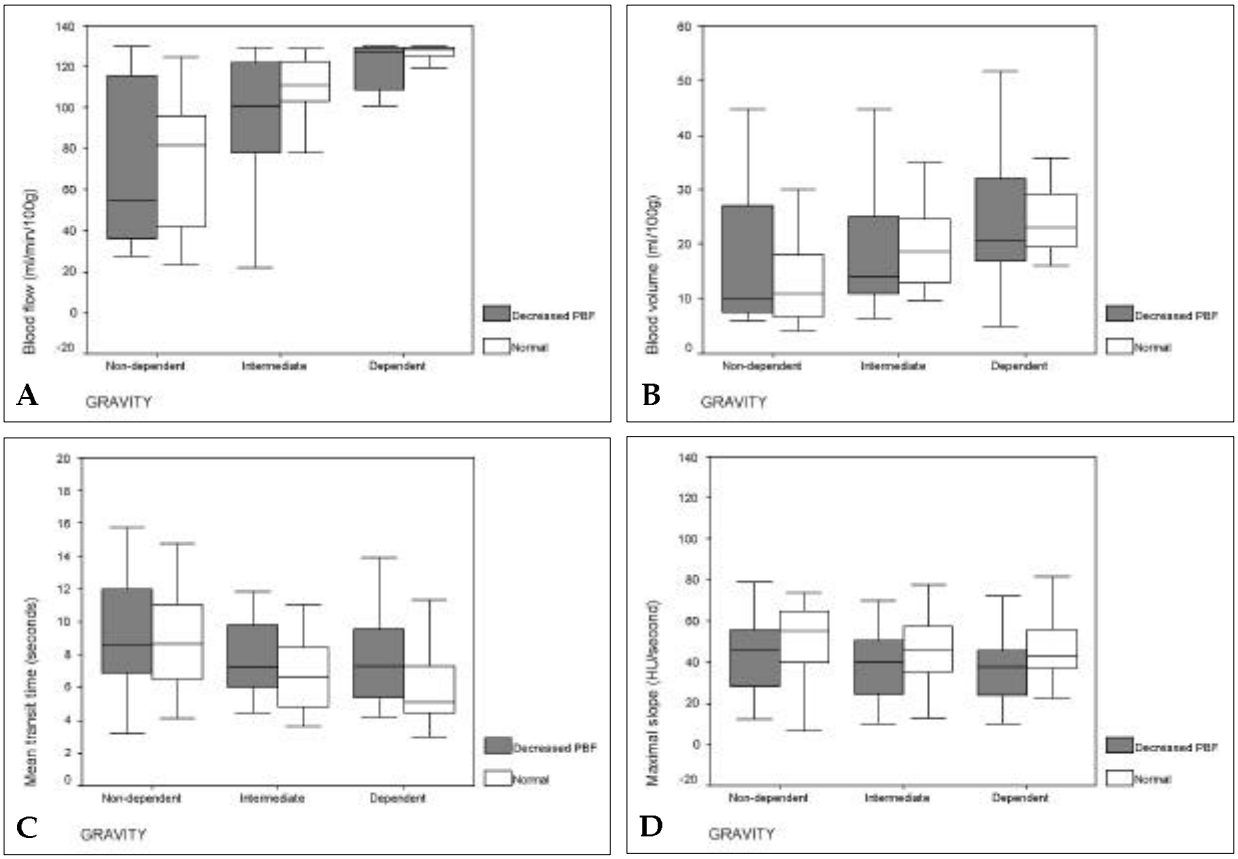

Fig. 5. Changing pattern of perfusion parameters including blood flow (A), blood volume (B), mean transit time (C), maximal slope (D) with respect to gravity in the decreased pulmonary blood flow (PBF) model versus baseline values. Summary plot based on median and quartiles. The box represents the interquartile range, which contains 50% of all values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. The line across the box indicates the median.

Increased pulmonary vascular resistance model

In the 8 lungs of 4 dogs, BF, BV, and MS in the increased PVR model showed significant reductions versus baseline (75.27 ± 24.44 ml/min/100g < 98.07 ± 16.79 ml/min/100g, p=0.000) (13.23 ± 9.74 ml/100g < 17.59 ± 6.71 ml/100g, p=0.007) (39.75 ± 17.32 HU/second < 48.89 ± 19.78 HU/second, p=0.000). MTT showed a slight increase, but without significance (6.45 ± 2.00 seconds > 6.06 ± 2.24 seconds, p=0.533).

Changes of perfusion parameters with respect to gravity

In the decreased PBF model, dependent and intermediate lung areas showed significant BF reductions (p=0.027, 0.036 respectively). All lung areas showed no change in BV but significant MS reductions (p<0.005). MTT increased in the dependent (p=0.042) and in the intermediate area (p=0.063) (Fig. 5). In the increased PBF model, no significant change in perfusion parameters was observed in any area (Fig. 6). In the increased PVR model, non-dependent area showed a significant change only in MTT, which decreased. Dependent and intermediate areas showed significant reductions in BF, BV, and MS (p<0.05). In these areas, MTT increased slightly, but without statistical significance. MTT was longer in the dependent area than in the non-dependent area, which was the inverse of MTT change with respect to gravity in the normal hemodynamic state, which is longer in the non-dependent area than in the dependent area (Fig. 7). In summary, BF reduced in both the decreased PBF model and in the increased PVR

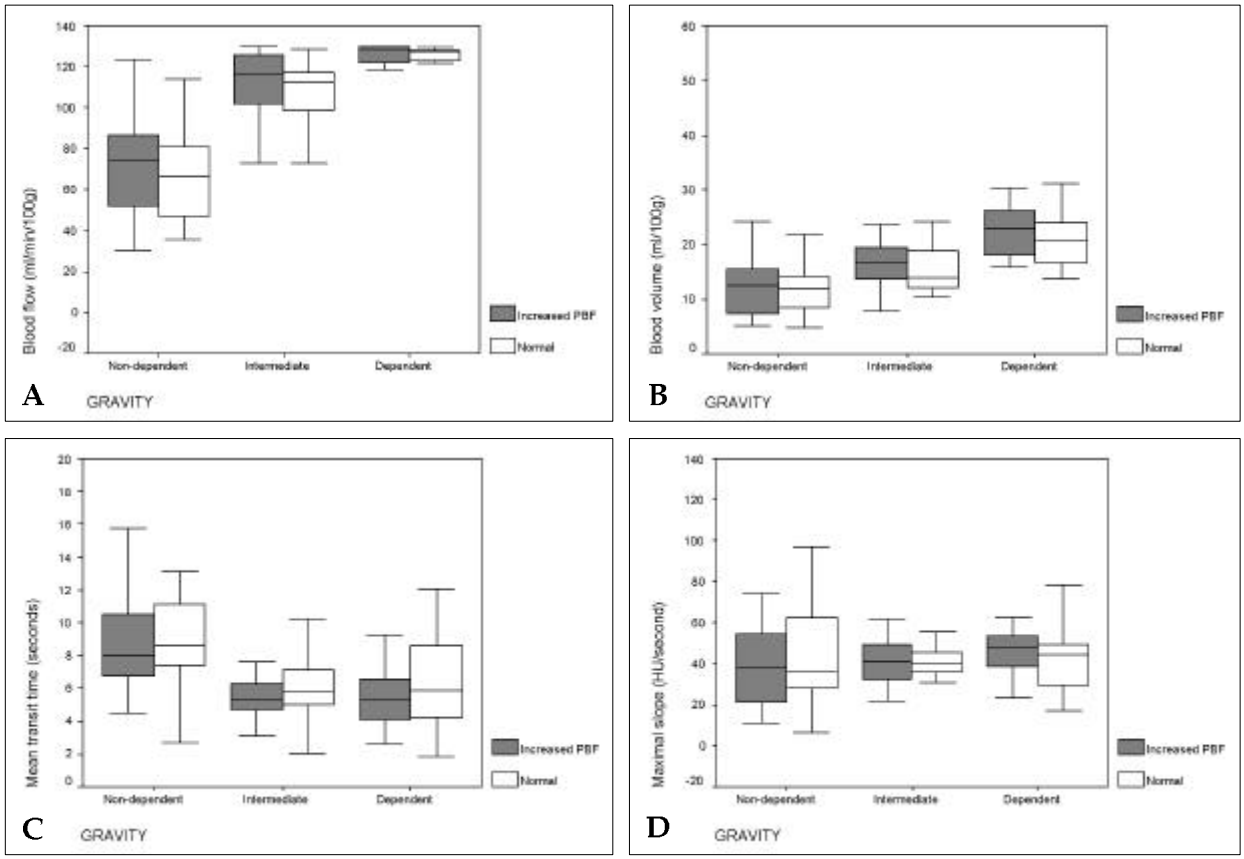

Fig. 6. Changing patterns of perfusion parameters, including blood flow (A), blood volume (B), mean transit time (C), maximal slope (D) with respect to gravity in the increased pulmonary blood flow (PBF) model versus baseline values. Summary plot based on median and quartiles. The box represents the interquartile range, which contains 50% of all values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. The line across the box indicates the median.

model. However, BV reduced only in the increased PVR model. MTT increased in the decreased PBF model, and changed heterogeneously in the increased PVR model, i.e., it increases in the dependent area and decreased in the non-dependent area. The greater BF reduction observed in the dependent area of the increased PVR model versus the decreased PBF model was attributed to a greater BV reduction.

Correlations of CT perfusion parameters with invasively measured hemodynamic parameters

The cardiac output of the right ventricle, measured by the thermodilution technique, increased slightly, when one pulmonary artery was occluded and decreased markedly in the increased PVR model (Table 1). PVR calculated from invasively measured hemodynamic parameters was found to be negatively correlated with BF by CT (p=0.001). MTT showed negative correlation with PVR only in the non-dependent area. A tentative positive correlation was found between invasively measured cardiac output and the amount of blood flow of the lung, calculated by multiplying the mean blood flow per volume per minute by the whole lung volume), but this was not significant (Fig. 8). CT values for cardiac BF over the whole lung per minute were smaller than invasively measured cardiac output values especially when the BF increased.

DISCUSSION

Recently, the quantification of pulmonary per-

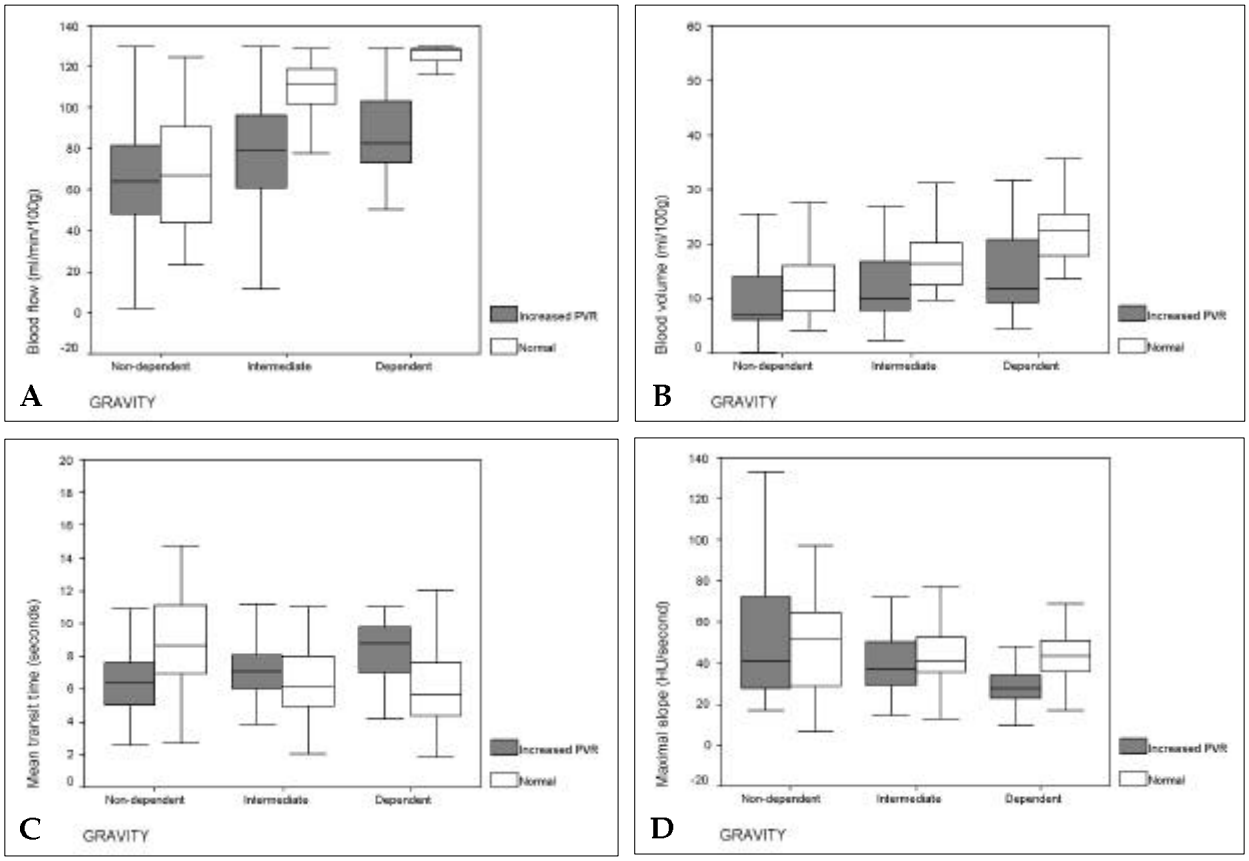

Fig. 7. Changing patterns of perfusion parameters including blood flow (A), blood volume (B), mean transit time (C), maximal slope (D) with respect to gravity in the increased pulmonary vascular resistance (PVR) model versus baseline values. Summary plot based on the median and quartiles. The box represents the interquartile range, and contains 50% of all values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. The line across the box indicates the median.

fusion has been studied non-invasively using CT.[12-17] Although, imaging with spiral CT does not permit electrocardiographic gating, due to a relatively low temporal resolution of 1 second, unlike electron beam CT, which has a scan time of 100 milliseconds, the effect of different cardiac phases on the quantification of pulmonary perfusion is not great. When the single compartment model is used for the quantification of perfusion using CT, two important assumptions are made.[12,17,18] First, only one compartment of the vascular space exists and the administered contrast material is confined within this space. Second, a bolus injection of contrast material is used.

However, extravascular contrast material rapidly extravasates by diffusion into extravascular and extracellular interstitial space.[20] Therefore, the assessment of perfusion in a parenchymal organ, other than brain, which has a blood-brain barrier, is impossible or inaccurate. Nevertheless, lung perfusion can be assessed using extravascular contrast material and single compartment model, because the lung is inflated with air and the interstitium is minimally developed compared to the capillaries responsible for effective gas-exchange with air. Intravascular contrast agent is being developed, but has not been used in clinical practice.

It is well known that lung perfusion is normally affected by gravity and that blood volume, and blood flow is higher in the dependent zone than in the non-dependent zone.[21] The present study shows the same distribution of perfusion parameters with respect to gravity in the normal hemodynamic state. In the decreased PBF model,

Table 1. Invasively Measured Cardiac Output and Pulmonary Vascular Resistance

Dog	Model	CO (L/min)	MPA-Pr (mmHg)	WP (mmHg)	PVR (Wood Unit)
1	Normal	1.4	12	4	5.93
	PBF	1.5	14	5	6.04
	PVR	1	20	4	15.69
2	Normal	1.4	17	7	7.09
	PBF	1	17	12	5.26
	PVR	0.8	25	9	19.28
3	Normal	1	12	7	5.05
	PBF	0.9	17	9	8.7
	PVR	0.8	25	6	22.62
4	Normal	1.3	16	2	10.94
	PBF	1.4	15	2	9.1
	PVR	1.4	28	2	18.57
5	Normal	0.8	9	7	2.44
	PBF	1.1	8	3	4.67

CO, cardiac output of right ventricle; MPA-Pr, mean pressure of main pulmonary artery; WP, wedge pressure of pulmonary artery; PVR, pulmonary vascular resistance; PBF, pulmonary blood flow.

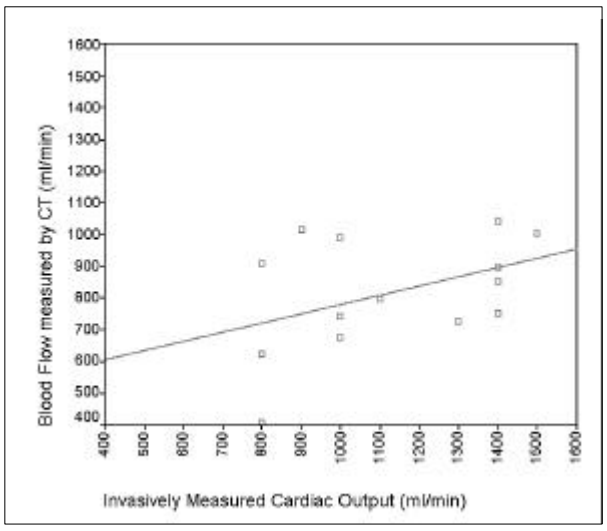

Fig. 8. Correlation between invasively measured cardiac output and the amount of blood flow in the lung, calculated by multiplying the mean blood flow per unit volume by the lung volume. r=0.456, p=0.218.

blood flow was reduced mainly due to a shorter mean transit time, without a significant change in blood volume. However, in the increased PBF model, blood flow increased due to a slightly longer mean transit time and a slightly reduced blood volume. These results mean that an acute reduction in the flow by proximal stenosis of the pulmonary artery does not cause any change in the peripheral vascular space, but that increased flow induces an expansion of the vascular space. However, no significant increase in blood flow was detected in the increased PBF model.

In the increased PVR model, peripheral pulmonary arterioles were occluded by infusing 50μm gelfoam powder. Significant reductions in blood flow and blood volumes were induced in the intermediate and dependent zones, but the mean transit time increased in the dependent zone and decreased in the non-dependent zone. The increment pattern of mean transit time with respect to gravity in the normal state was reversed in the increased PVR model. This was a unique phenomenon in MTT in increased PVR model, compared to other parameters that showed the same increase/ decrease pattern as the normal state in terms of gravity effects despite increases or decreases compared to the normal state. Decreased

mean transit time in the non-dependent zone of the PVR model suggests the existence of a compensatory mechanism to increase and redistribute blood flow to the non-dependent, low vascular-resistance zone. The mechanism of redistribution of blood flow may be due to different extent of interstitial edema, capillary recruitment or inhomogeneous gelfoam infusion due to gravity. These findings suggest that blood flow is redistributed to the zones with relatively low vascular resistance, which can be distinguished from the zones of reduced blood flow without increased vascular resistance by a shorter mean transit time

These results can be summarized by a simple formula (Table 2). However, they cannot be applied directly to the interpretation of perfusion CT images because normal reference values of perfusion parameters are not available. In terms of the normal values of perfusion parameters, the effects of gravity on these parameters should be taken into account to enable direct comparisons between corrected normal values and a patient's corrected values. Pulmonary vascular resistance is usually calculated from data obtained by catheterization using Poseulle's equation, which written as:-

Poiseulle's equation: $Q = \frac{p(Pi - Po)r^4}{8ml}$

(Q=flow volume, Pi=inflow volume, Po=outflow volume, r=radius of tube, μ=viscosity, l=length of tube)

Pulmonary vascular resistance is theoretically inversely proportional to the total cross-sectional areas of the pulmonary arteries. However, this concept cannot be applied in vivo due to many confusing factors. Arterial flow is pulsatile, sometimes non-laminar, the arterial walls can constrict or dilate, blood is not homogenous, and the arterial tree has generally a tapering and branching pattern. In addition, capillary recruitment phenomena affect pressure and flow, and make it difficult to measure and calculate vascular resistance *in vivo*. Nevertheless, the invasive catherization method continues to be used to evaluate pulmonary vascular resistance, because of its high reproducibility, the wealth of clinical data available, and the lack of a suitable substitute. Therefore, noninvasive measurements of perfusion parameters by CT perfusion studies offer a valuable substitute and perhaps a better modality for accurately evaluating regional pulmonary perfusion.

This study is limited with respect to the measurements of lung density and input and output function. Vessels exceeding 1 mm in diameter could not be completely excluded from the region of interest. One study reported upon the separated contribution made by small arteriolar density to the density of the region of interest by deconvolution of time-density curve.[17] The mean transit time is dependent only on input function, and blood volume is dependent on both input and output function. The measurement of the input or output functions of different vessels may affect the values of perfusion parameters. So, reference vessels for the measurement of input and output fuction should be same in all measurements, but this is not always possible in practice due to different levels of scanned slices and individual anatomic differences. In the decreased and increased PBF models, we defined lung contralateral to the decreased PBF model as the increased PBF model. However, flow increase in increased PBF model was insufficient versus the normal state to be statistically significant. The hemodynamic models used in this study do not wholly represent the pathophysiologic status of chronic hemodynamic changes, particularly variables resulting

Table 2. Simplified Changes of Perfusion Parameters According to Hemodynamic Status

Hemodynamic status	Perfusion parameters
Increased PBF	BF ↑ = BV ↑ / MTT ↓
Decreased PBF	BF ↓ = BV → / MTT ↑
Increased PVR	BF ↓ = BV ↓ / MTT ↑

PBF, pulmonary blood flow; PVR, pulmonary vascular resistance; BF, blood flow; BV, blood volume; MTT, mean transit time.

from collateral development, although the main pathophysiologies of flow and pressure change were adequately represented by our experiment. In addition, any possibility of air-trapping or volume loss, which might be variable between scans and affect density measurements, was not considered in our study.

In conclusion, the noninvasive evaluation of pulmonary perfusion and the analysis of its hemodynamic status are feasible by CT perfusion scanning. In clinical practice, parenchymal lung density measured on CT images represents blood volume.[2-7] Low density areas of lung in static CT image may thus be considered as areas of reduced blood volume, without information about flow or vascular resistance. Density differences between normal and attenuated flow areas are not often apparent in contrast enhanced static CT scans. The meticulous analysis of perfusion parameters provides useful information about flow and vascular resistance. Based on an understanding of perfusion characteristics in the normal state, information derived from perfusion parameters can be used to detect and evaluate abnormal regional hemodynamic changes in lung. Furthermore, the noninvasive estimation of pulmonary vascular resistance should be possible by thoroughly analyzing CT perfusion parameters. The absolute quantification of lung perfusion and a clinically feasible method of using CT perfusion scans require further study and verification.

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