Computed tomography correlates with cardiopulmonary hemodynamics in pulmonary hypertension in adults with sickle cell disease

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Abstract: Our objective was to determine whether computed tomography angiography (CTA) measurements of pulmonary artery size can noninvasively assess hemodynamics and diagnose pulmonary hypertension (PH) secondary to sickle cell disease (SCD). Twenty SCD patients with confirmed PH were compared with 20 matched controls. Diameters of the pulmonary artery trunk and branches were measured with CTA and a semiautomatic segmentation algorithm. Measurements were normalized by body size and correlated (Spearman rank) with hemodynamic markers from right-heart catheterization. Receiver operating characteristic (ROC) curves were used to investigate the role of pulmonary artery sizes in diagnosing PH. Analysis of pulmonary artery sizes adjusted for body surface area (BSA) resulted in the most significant discrimination between subjects with PH secondary to SCD and controls ($P < 0.001$); PH was diagnosed accurately with an area under the ROC curve of 0.99. There was significant correlation between pulmonary artery sizes and body mass index (BMI) and BSA only in controls ($r = 0.46$ – 0.68 , $P < 0.04$ for all). The most significant correlations with hemodynamic markers were found between BMI-adjusted pulmonary artery sizes and high systolic pulmonary arterial pressure, high pulmonary vascular resistance, high systemic vascular resistance, and low cardiac output ($r = 0.47$, 0.62 , 0.61 , and 0.66 , respectively; $P < 0.04$ for all). BMI-adjusted CTA measures of the pulmonary artery relate to high pulmonary vascular resistance and reduced cardiac output in patients with SCD and PH. CTA with quantitative image analysis is a powerful noninvasive diagnostic tool for PH in SCD and shows promise as estimator of hemodynamic markers.

Keywords: CT angiography, cardiopulmonary hemodynamics, pulmonary hypertension, sickle cell disease, arterial size, quantitative imaging.

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INTRODUCTION

Pulmonary hypertension (PH) is a progressive vascular disease that is one of the strongest predictors of death among adults with sickle cell disease (SCD).¹⁻⁸ SCD patients present with a number of cardiopulmonary abnormalities, including chronically elevated mean pulmonary arterial pressures (mPAPs) that could indicate PH.^{9,10}

Autopsy studies have suggested that as many as 75% of patients with SCD have evidence of pulmonary vascular disease at the time of death. However, this may be an overestimate based on the high number of sudden death events evaluated in this cohort.¹¹ Moreover, approximately one-third of adult SCD patients present noninvasive echocardi-

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ographic findings related to PH,^{9,12} and as described below, 6%–10% have PH by right-heart catheter assessments.^{1,5-7,13}

Right-heart catheterization (RHC) is the gold standard for the diagnosis and hemodynamic assessment of PH, although it is invasive and carries some risk for complications.^{14,15} Clinically, PH is defined by mPAP $\geq$ 25 mmHg via RHC. Alternatively, Doppler echocardiography has frequently been used for noninvasive screening for PH.⁶ Elevated tricuspid regurgitant velocity (TRV $\geq$ 2.5 m/s), measured by echocardiography, is associated with increased risk of death among SCD patients.¹ Although TRV correlates with increased pulmonary arterial pressure, its sensitivity and specificity in detecting PH vary, depending on the cutoff value; studies have shown indications of abnormal TRV in 32% and 9% of SCD cases, using 2.5- and 3.0-m/s cutoffs, respectively, while the presence of PH in 6%–10% of SCD cases was confirmed by the more direct measurement of pulmonary arterial pressure by RHC.^{1,5-7,13}

In the past, studies have investigated the use of pulmonary computed tomography angiography (CTA), in the diagnosis and assessment of PH secondary to a number of diseases.^{2,16-20} Noninvasive image data are an attractive alternative to RHC, particularly for patients who have CTA scans available before RHC as part of their routine clinical assessment for PH and other cardiopulmonary diseases. Such imaging studies have elucidated the substantial changes in pulmonary vasculature that occur as a consequence of PH, including pulmonary trunk and main artery dilation and pruning or tapering of the blood vessels (large arterial trunk and abrupt transition from large to small arteries).^{2,17,20} Furthermore, manual measurements of pulmonary artery (PA) size from CT images have been shown to correlate well with PA pressures, potentially providing an alternative, noninvasive method of evaluating PH.^{16,21} Grubstein et al.¹⁶ investigated PA size only in relation to the systolic pressure and forced expiratory value in the first minute. The study by Edwards et al.²¹ did not analyze the correlations between PA sizes and hemodynamics, nor did it match patient and control populations. In addition, the manual measurements of PA size in both these studies suffer from 2-dimensional projections, which estimate only actual 3-dimensional PA size and thus may not be reproducible.²

Recent advancements in computer-aided analysis of CTA have provided accurate and reproducible segmentation and quantification of the 3-dimensional PA structure.² In this study, we leveraged a previously developed computer-based tool for CTA to accurately and reproducibly quantify the 3-dimensional structures of the pulmonary trunk and main pulmonary branches.² The two

main objectives of the study were (1) to evaluate the role of CTA-derived PA size as a noninvasive diagnostic and prognostic indicator of PH secondary to SCD²² and (2) to investigate the relationship between CTA-derived PA size and the hemodynamic profile in patients with PH.⁵ Overall, we aim to define the methodology of noninvasive, semiautomated analysis of CTA in studying the anatomic and hemodynamic changes linked to PH.

METHODS

Study population

This retrospective study follows HIPAA (Health Insurance Portability and Accountability Act) compliance standards. The project was Institutional Review Board exempt and was approved by the National Institutes of Health's Office of Human Subjects Research, and thus informed consent was waived.

We identified 64 SCD patients who were admitted to the National Institutes of Health and received RHC for hemodynamic management. Of these 64 eligible patients, 44 had confirmed PH (mean PA pressure $\geq$ 25 mmHg from RHC). Only 24 of these patients underwent pulmonary CTA and were considered for inclusion in the study. Four of these 24 patients were excluded after visual inspection because of poor bolus enhancement and/or major imaging artifacts on CTA data. This resulted in a sample of 20 PH cases: 5 men and 15 women with a mean age of 42 ± 12 years (range: 18–59). All cases were homozygous for the sickle cell allele, and all but 2 cases (one white and one Hispanic) were African American. Only 18 of these 20 patients were also evaluated with transthoracic echocardiography.

For diagnostic-accuracy assessment, we randomly selected 20 controls without SCD, PH, or a primary diagnosis of lung pathology. Controls had CTA data acquired and were matched to PH cases on the basis of age (within 3 years) and sex (5 men and 15 women). The mean age of controls was 43 ± 12 years (range: 21–62); 11 were white and 9 were African American. Controls were evaluated clinically for the following conditions: B-cell lymphoma, metastatic colorectal cancer, brain lesions, breast cancer, myelodysplastic syndrome, meningioma, synovial sarcoma, melanoma, von Hippel-Lindau disease, Cushing's syndrome, TTF-1 mutation/NKX2-1 haploinsufficiency syndrome, cutaneous T-cell lymphoma, and hepatitis.

Given our sample size of 20 cases with SCD/PH and 20 age and sex-matched controls, a clinically meaningful paired difference in main PA diameter of at least 1.5 mm could be detected at 90% power, using a significance level of 0.05 and a 2-sided, paired *t* test assuming a common

group standard deviation of 3 mm (based on results published by Edwards et al.²¹) and a paired correlation of 0.8.

Pulmonary CTA

All pulmonary CTA data were acquired with GE Lightspeed Ultra (GE Healthcare, Milwaukee, WI), Philips Mx8000 IDT 16 or Brilliance 64 (Philips Medical Systems, Cleveland, OH), or Siemens Definition (Siemens Medical Solutions, Malvern, PA) and analyzed retrospectively. CTA images were acquired at a fixed tube voltage of 120 kVp. Tube current varied between 230 and 390 mA s. Isovue contrast agent was delivered at a rate of 4–5 mL/s. Image resolution ranged from 0.63 to 0.88 mm in the axial view and from 1 to 1.25 mm in slice thickness. SCD patients were referred for CTA for management of suspected or confirmed PH, while controls were mainly referred for CTA for assessment of suspected thromboembolism secondary to the underlying primary pathology.

Right heart catheterization

Standard Swan-Ganz RHC was performed on all SCD patients, with cardiac output measured by thermodilution (Baxter Healthcare, Deerfield, IL) within 3 days of CT evaluation, and analyzed retrospectively. The cutoff for PH diagnosis was mPAP $\geq$ 25 mmHg.

Echocardiography

Transthoracic echocardiography was performed on 18 of the eligible SCD patients with the Acuson Sequoia (Siemens-Acuson, Mountain View, CA) or the Sonos 5500 (Philips, Andover, MA) and analyzed retrospectively. TRV was assessed in the parasternal right ventricular inflow, parasternal short axis, and apical 4-chamber views, and a minimum of 5 sequential complexes were recorded. Our study used the recorded peak TRV. This procedure was performed within 1 day of CT evaluation.

CTA image processing

Pulmonary trunk and branch sizes were quantified from CTA data with a semiautomated segmentation algorithm that requires minimal user initialization; the technique has previously been published.² The algorithm was initialized by manually placing 3 seed points on the CTA image: one in the PA trunk at the level of the primary bifurcation and one in each of the right and left pulmonary main arteries before the secondary bifurcation. The PA vessels were then automatically segmented with level sets, adaptive surfaces that expand from the seed points

to the edges of high contrast in the image.^{23,24} Arterial lumen distension (PA size) was calculated by computing a centerline along the trunk and main arteries and measuring the Euclidean distance from the centerline to the vessel wall. The maximum distension of the lumen in the PA trunk and main arteries (maximum over left and right arteries) was reported by the algorithm.

To validate the segmentation algorithm, two observers manually measured the diameters of the PA trunk and the right and left pulmonary main arteries for the CTA cases (PH and controls). Observers were research interns trained to perform PA measurements by an experienced interventional radiologist. Each observer was blinded to the patient diagnosis and the other available measurements. Then semiautomatic and manual measurements of PA were compared by the method of Bland and Altman.²⁵ Numerical results in this article were obtained with the semiautomatic algorithm.

Statistical analysis

Accuracy of CT-derived PA size in PH diagnosis was assessed in 40 patients (20 PH cases, 20 controls) by means of a multivariate logistic regression, which modeled PH diagnosis as a response to PA size while adjusting for age and sex. Receiver operating characteristic (ROC) curves were then constructed on the basis of regression-based probabilities, and the area under the curve (AUC) was recorded.²⁶ The operating point on the ROC curve with maximum accuracy (defined as the sum of sensitivity and specificity) was selected to provide clinically meaningful diagnostic cut points.

To account for the relationship between body size and blood vessel size, we investigated the correlation between PA size and patient's body surface area (BSA, calculated with the formula of DuBois and DuBois²⁷) and body mass index (BMI), two popular indices of body size. Monotonic relationships between PA sizes and BSA or BMI were evaluated with the nonparametric Spearman rank correlation, so as not to assume any underlying statistical distributions and linear relationships between variables, particularly for a small sample size. Then we indexed the PA sizes by dividing by BSA or BMI. Additional logistic regression and ROC analyses were performed for BSA- and BMI-indexed PA sizes. ROC curves were compared on an AUC basis by means of the nonparametric approach of DeLong et al.,²⁸ with Bonferroni correction.

Wilcoxon rank-sum tests assessed the paired differences in body and PA sizes between PH cases and controls. The monotonic relationships between hemodynamic markers (including the cardiac output and the pulmonary

vascular resistance) and the PA sizes (including indexed sizes) of the 20 PH patients were also evaluated via Spearman rank correlation. Two-sided hypotheses were constructed for all statistical tests, and the significance level was set at 0.05, except when multiple comparisons were considered. All statistical analyses were carried out with SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

Validation of segmentation

There was no significant interobserver variability in measuring either the PA trunk (PT) or the main PA branches

(PB). Bland-Altman analysis showed 95% limits of agreement spanning 8.1 mm for PT and 5.7 mm for PB (Fig. 1). There were no significant differences between observer 1 and semiautomatic measurements (here referred as to computer-aided diagnosis, or CAD) for PT and PB or between observer 2 and CAD PB measurements. The only significant difference occurred between the estimations of PT by observer 2 and CAD ($P = 0.05$). Bland-Altman analysis for both observers showed that mean differences between the two methods (manual and CAD) were less than 1 mm. The 95% limits of agreements for PT were 7.1 mm for observer 1 and CAD and 9.8 mm for observer 2 and

Figure 1. Bland-Altman plots comparing observer-CAD (computer-aided diagnosis) performance for observer 1 (a) and observer 2 (b), and interobserver variability (c) in measuring the pulmonary trunk (PT) and main pulmonary branches (PB). In each plot, the differences are plotted against average measurements of the corresponding two methods, in millimeters. The mean difference between the two methods is represented by a solid gray line; dashed lines represent the 95% limits of agreement (1.96 SD). The solid black line represents the zero baseline.

CAD. For PB, the limits of agreements were 5.8 mm for observer 1 and CAD and 6.2 mm for observer 2 and CAD. Observer-CAD variability was comparable to the inter-observer performance ($P > 0.1$ for all).

Correlation between PA size and body size

Moderate to high correlations between PA sizes and both BMI and BSA were found in the control group (Table 1). Significant correlations were obtained between PA sizes and both BSA and BMI ($r = 0.68$ and 0.46 , $P = 0.001$ and 0.04 , respectively, for PT diameter; $r = 0.63$ and 0.60 , $P = 0.002$ and 0.01 , respectively, for PB diameter). The PH case group showed no significant correlation between PA diameter and BSA or BMI, although correlations with BSA were higher than those with BMI. The values of BSA and BMI did not vary significantly between PH patients and controls ($P > 0.09$ for both).

CT-based diagnostic accuracy of PH

Mean CT-derived PT and PB diameters were significantly different ($P < 0.001$) between PH cases (PT: 33.73 ± 3.92 mm; PB: 25.17 ± 2.90 mm) and controls (PT: 27.03 ± 2.94 mm; PB: 20.62 ± 3.06 mm), as shown in Table 2. When indexed by body size via BMI and BSA, PT and PB diameters were also significantly different between the two groups (all $P < 0.001$).

ROC analysis showed that CT-derived PA size provided good discrimination of PH secondary to SCD among subjects (Figs. 2, 3). The AUC was 0.95 (95% confidence interval [CI]: 0.89–1.00) when nonindexed PT diameter was used as a predictor. Diagnostic performance was improved when BSA-indexed PT diameter was used to predict PH (AUC: 0.99 [95% CI: 0.97–1.00]) but decreased when BMI-indexed PT diameter was used in prediction (AUC: 0.88 [95% CI: 0.78–0.98]). However, pairwise comparison of either BMI- or BSA-indexed PT diameters with nonindexed PT diameter showed no significant difference in diagnostic

prediction ($P > 0.2$ for both). A significant difference was noted between the performances of BMI- and BSA-indexed PT diameters ($P = 0.02$). With BSA-indexed PT diameter, the best accuracy for diagnosing PH was obtained with a cutoff value of 12.12 mm/m², which yielded sensitivity of 0.95 and specificity of 0.95.

CT-derived PB diameter as a predictor of PH showed similar trends in the ROC analysis, as shown in Figure 3. The AUC was 0.93 (95% CI: 0.85–1.00) with nonindexed PB diameter as diagnostic predictor. BSA-indexed PB diameter provided better diagnostic performance (AUC: 0.96 [95% CI: 0.90–1.00]), but BMI-indexed PB diameter did not (AUC: 0.86 [95% CI: 0.74–0.97]). There were no significant differences in pairwise comparisons of BMI- or BSA-indexed PB diameter with nonindexed PB diameter ($P > 0.2$ for both), but there was a significant difference between BSA-indexed and BMI-indexed PB diameters in diagnostic prediction ($P = 0.03$). The best diagnostic accuracy was obtained with a BSA-indexed PB diameter of 9.44 mm/m² (sensitivity: 90%, specificity: 85%).

Correlation between PA size and pulmonary hemodynamic markers

The largest number of significant correlations between CT-derived PA size and the hemodynamic markers from RHC and transthoracic echocardiography evaluation was observed for vessel diameters indexed by BMI. The correlations and their significance for 20 SCD patients (18 for TRV) are shown in Table 3. A moderate but significant correlation between systolic PA pressure and BMI-indexed PB diameter was found ($r = 0.47$; $P = 0.04$). However, no significant relationships between BMI-indexed PB diameter and mean PA pressure existed ($P = 0.14$). Furthermore, no significant correlations between BMI-indexed PT diameter and pulmonary pressures (systolic, diastolic, and mean PA pressures) were found in this study population.

Table 1. PA sizes in relation to body size parameters

Characteristic	PH cases		Controls		PH cases and controls	
	BMI	BSA	BMI	BSA	BMI	BSA
PA trunk diameter	0.32 (0.18)	0.40 (0.09)	0.46 (0.04)*	0.68 (0.001)*	0.21 (0.20)	0.18 (0.26)
Main PA branch diameter	−0.05 (0.50)	0.16 (0.50)	0.60 (0.01)*	0.63 (0.002)*	0.14 (0.40)	0.10 (0.55)

Note: Data are Spearman correlation coefficient (P value). PA: pulmonary artery; PH: pulmonary hypertension; BMI: body mass index; BSA: body surface area.

* Statistically significant correlation ($P \leq 0.05$).

Table 2. Body and pulmonary artery sizes in PH cases and controls

Characteristic	PH cases	Controls	<i>P</i> value
Body mass index (BMI), kg/m ²	26.51 ± 4.35	29.95 ± 8.92	0.27
Body surface area (BSA), m ²	1.80 ± 0.23	1.98 ± 0.31	0.09
Pulmonary trunk diameter (PT), mm	33.73 ± 3.92	27.03 ± 2.94	<0.001
Main pulmonary branch diameter (PB), mm	25.17 ± 2.90	20.62 ± 3.06	<0.001
BMI-indexed PT, mm m ² /kg	1.30 ± 0.22	0.95 ± 0.20	<0.001
BSA-indexed PT, mm/m ²	18.96 ± 2.45	13.86 ± 1.64	<0.001
BMI-indexed PB, mm m ² /kg	0.97 ± 0.19	0.72 ± 0.15	<0.001
BSA-indexed PB, mm/m ²	14.20 ± 2.21	10.54 ± 1.45	<0.001

Note: Data are presented as mean ± standard deviation. *P* value represents the result of the Wilcoxon rank-sum tests to assess the paired differences in a given observation between PH cases and controls. PH: pulmonary hypertension.

Pulmonary capillary wedge pressure was inversely correlated with BMI-indexed PA size, but the relationship was not significant ($P > 0.32$). Significant inverse relationships were observed between cardiac output and both BMI-indexed PT ($r = -0.62$, $P = 0.006$) and PB ($r = -0.66$, $P = 0.003$) diameters. Moderate and significant monotonic relationships between BMI-indexed PT diameter and both pulmonary vascular resistance ($r = 0.69$, $P = 0.002$) and systemic vascular resistance ($r = 0.57$, $P = 0.01$) were

also observed. Similar relationships existed between BMI-indexed PB diameter and both pulmonary vascular resistance ($r = 0.62$, $P = 0.006$) and systemic vascular resistance ($r = 0.61$, $P = 0.008$). The correlation between TRV and BMI-indexed PT diameter was found to be moderate but significant ($r = 0.49$, $P = 0.03$). A direct but nonsignificant relationship was observed between TRV and BMI-indexed PB diameter ($r = 0.3$, $P = 0.22$).

Correlations using no indexing and BSA indexing of PA size are shown in Table 4. The only significant correlation with the hemodynamic markers when PA size was not indexed by body size was observed for central venous pressure ($r = 0.46$, $P = 0.05$). For BSA-indexed PT diameter, the only significant correlation observed was with TRV ($r = 0.57$, $P = 0.01$). In addition, BSA-indexed PB diameter showed only a moderate and significant inverse correlation with cardiac output ($r = -0.48$, $P = 0.04$). Finally, a significant inverse relationship ($r = -0.81$, $P < 0.0001$) was recorded between the cardiac output and the pulmonary vascular resistance of the 20 PH patients.

Figure 2. Comparison of receiver operating characteristic curves using computed tomography-derived pulmonary artery trunk (PT) size with and without indexing by body size measurements. Area-under-the-curve values for the detection of pulmonary hypertension were 0.95, 0.99, and 0.88 when nonindexed, body surface area (BSA)-indexed, and body mass index (BMI)-indexed PT diameter, respectively, were used as the predictor.

DISCUSSION

We showed significant correlations between PA and body sizes on healthy controls. Unsurprisingly, these correlations were not uniformly observed for PH patients, because the chronic increase of blood pressure results in major changes in the size and structure of the PA but not in correlated changes in body size. This means not only that cases are differentiated from controls by PA size but also that the changes are complex and multifactorial and not simple, predictable dilations. This could possibly reflect changes that either cause or are markers of PH, such as vascular remodeling and pruning of the pulmo-

Figure 3. Comparison of receiver operating characteristic curves using computed tomography-derived main pulmonary branch (PB) size with and without indexing by body size measurements. Area-under-the-curve values for the detection of pulmonary hypertension were 0.93, 0.96, and 0.86 when nonindexed, body surface area (BSA)-indexed, and body mass index (BMI)-indexed PB diameter, respectively, were used as the predictor.

nary branches, in addition to changes in vessel thickness and lumen size. The fact that BSA and BMI parameters did not differ significantly between PH cases and controls suggests that the observed differences in PA size between the groups are not due to differences in patients' body habitus. Therefore, the body size indexing of vessel sizes is appropriate to assess PH in these patients independent of hemodynamic markers.

CT-based diagnosis of PH

Our study shows that PA size computed from CTA has the potential to be an indicator of PH, particularly when we account for the relationship between body size and PA size. The increased accuracy of the BSA-adjusted PA sizes relative to unadjusted values is supported by the fact that there is a link between body size and blood pressure.²⁹ As a result, the BSA-adjusted PA sizes were the most accurate PH diagnostic marker, with AUC = 0.99.

Although our study applies primarily to secondary PH in SCD, observations made in previous studies investigating PH across many primary diagnoses¹⁶ suggest that PA size is a powerful marker not only for the assessment of PH in general but also in the consideration of specific, primary diagnoses, such as SCD. This, however, does not necessarily imply that PA sizes observed in PH secondary to other diseases would differ from those of controls in

the same way as in PH secondary to SCD. These differences may be more or less pronounced when examined in the context of another disease. These conjectures emanate from the fact that the multiple etiologies of PH have a variety of associated mechanisms.³⁰ Certainly, some entities may have acute or chronic components that differ, and the PA size changes may likewise differ with the degree of chronicity. Such a phenomenon has been described in the portal vein with advancing degrees of cirrhosis-induced portal hypertension, whereby a portal vein may not be free to fully dilate in response to elevated pressures in chronic settings because of a constricting stiff liver or vessel wall.³¹ The pulmonary vasculature may be free to dilate without the constraints of an inelastic environment or restricted motion.

Correlation of PA size and hemodynamic markers

Among the hemodynamic markers, cardiac output, which is elevated in SCD as a physiological compensatory response to severe anemia, may be in some ways a more relevant indicator of cardiovascular disease in PH for SCD patients than pulmonary arterial pressures. This may be explained by the possible presence of other anatomical abnormalities that these patients have been shown to present, such as cardiac chamber enlargement, severely compromised right ventricular function, and tricuspid valve insufficiency.^{9,10} Such morphological abnormalities would certainly affect cardiac output, but it is unclear to what degree they may be contributing to this result. It is also unclear to what extent such abnormalities would directly influence PA size, if at all. Nevertheless, cardiac output had the most correlates with adjusted PA sizes in our study, with the highest correlation coefficients. It has been hypothesized that high cardiac output due to severe anemia contributes to both PA dilation and elevated PA pressure³² and that the long-term pathological response to very high PA flow leads to development of high pulmonary vascular resistance and clinically significant PH.³³ Our study found a significant inverse relationship between cardiac output and pulmonary vascular resistance in our patient population.

Both pulmonary and systemic vascular resistance correlated only with BMI-adjusted PA sizes. In general, the BMI-adjusted PA sizes proved to correlate with more hemodynamic markers than the BSA-adjusted ones; this is in contrast to the earlier observation that BSA-adjusted PA sizes were better diagnostic markers. One major difference in the two methods of indexing for body size is that the formula used to calculate BSA penalizes weight more heavily than that for BMI. Further, patients with

Table 3. Pulmonary hemodynamic profile and its relation to pulmonary artery size I

Characteristic	Mean $\pm$ SD	Spearman correlation coefficient (<i>P</i> value)	
		BMI-indexed PA trunk size	BMI-indexed PA main branch size
Systolic PA pressure, mmHg	61.40 $\pm$ 13.11	0.44 (0.06)	0.47 (0.04)*
Diastolic PA pressure, mmHg	26.40 $\pm$ 6.93	0.25 (0.31)	0.18 (0.48)
Mean PA pressure, mmHg	39.40 $\pm$ 7.64	0.36 (0.14)	0.35 (0.15)
Central venous pressure, mmHg	9.90 $\pm$ 3.80	-0.10 (0.70)	-0.07 (0.77)
Pulmonary capillary wedge pressure, mmHg	14.80 $\pm$ 4.47	-0.25 (0.32)	-0.16 (0.51)
Cardiac output, L/min	7.90 $\pm$ 2.07	-0.62 (0.006)*	-0.66 (0.003)*
Mixed venous oxygen saturation, %	68.70 $\pm$ 9.33	-0.23 (0.40)	-0.02 (0.93)
Peripheral oxygen saturation, %	95.30 $\pm$ 4.76	0.05 (0.87)	0.09 (0.74)
Systemic systolic blood pressure, mmHg	125.40 $\pm$ 16.21	-0.27 (0.28)	-0.32 (0.19)
Systemic diastolic blood pressure, mmHg	75.40 $\pm$ 12.35	-0.10 (0.70)	-0.19 (0.44)
Systemic mean blood pressure, mmHg	91.80 $\pm$ 13.08	-0.13 (0.60)	-0.25 (0.31)
Pulmonary vascular resistance, dyn s cm ⁻⁵	273.80 $\pm$ 129.53	0.69 (0.002)*	0.62 (0.006)*
Systemic vascular resistance, dyn s cm ⁻⁵	857.70 $\pm$ 199.90	0.57 (0.01)*	0.61 (0.008)*
Heart rate, beats/min	74.10 $\pm$ 13.79	0.03 (0.90)	-0.16 (0.52)
Tricuspid regurgitant velocity, m/s	3.60 $\pm$ 0.49	0.49 (0.038)*	0.30 (0.22)

Note: PA: pulmonary artery, BMI: body mass index.

* Statistically significant correlation ($P \leq 0.05$).

Table 4. Pulmonary hemodynamic profile and its relation to pulmonary artery size II

Characteristic	PA trunk size	PA main branch size	BSA-indexed PA trunk size	BSA-indexed PA main branch size
Systolic PA pressure	0.09 (0.71)	0.10 (0.69)	0.21 (0.40)	0.29 (0.24)
Diastolic PA pressure	0.09 (0.71)	0.09 (0.73)	0.31 (0.20)	0.19 (0.45)
Mean PA pressure	0.09 (0.70)	0.07 (0.77)	0.26 (0.30)	0.23 (0.36)
Central venous pressure	0.33 (0.18)	0.46 (0.05)*	0.02 (0.92)	0.02 (0.94)
Pulmonary capillary wedge pressure	-0.04 (0.89)	0.18 (0.47)	-0.13 (0.60)	-0.13 (0.61)
Cardiac output	0.01 (0.95)	-0.03 (0.91)	-0.42 (0.08)	-0.48 (0.04)*
Mixed venous oxygen saturation	0.09 (0.74)	0.46 (0.08)	-0.08 (0.76)	0.15 (0.60)
Peripheral oxygen saturation	0.03 (0.91)	0.14 (0.62)	-0.02 (0.94)	0.15 (0.59)
Systemic systolic blood pressure	0.13 (0.60)	0.12 (0.64)	-0.31 (0.20)	-0.36 (0.13)
Systemic diastolic blood pressure	0.22 (0.38)	0.20 (0.42)	-0.23 (0.36)	-0.31 (0.20)
Systemic mean blood pressure	0.140 (0.58)	0.09 (0.71)	-0.30 (0.23)	-0.40 (0.10)
Pulmonary vascular resistance	0.10 (0.68)	-0.01 (0.95)	0.40 (0.10)	0.37 (0.13)
Systemic vascular resistance	-0.04 (0.88)	0.04 (0.86)	0.17 (0.48)	0.29 (0.23)
Heart rate	-0.08 (0.75)	-0.32 (0.20)	-0.16 (0.55)	-0.25 (0.32)
Tricuspid regurgitant velocity	0.45 (0.06)	0.09 (0.71)	0.57 (0.01)*	0.40 (0.09)

Note: Data are Spearman correlation (*P* value). PA: pulmonary artery, BSA: body surface area.

* Statistically significant correlation ($P \leq 0.05$).

SCD have characteristic fat deficits that might alter the interpretations of BSA and BMI.

TRV correlated significantly with both adjusted forms of PT size but with no forms of PB size. This makes intuitive sense, given that the PT is directly in closer series with the right ventricle and that the PB may reflect rapid tapering or pruning, which is characteristic of advanced PH. These correlations may provide insight into what directly and physically causes elevated TRV, which by itself is a marker of increased risk of death but may overestimate right ventricular pressure and PH. This result synthesizes and further supports the results of previous studies that separately linked TRV and PT size to the presence of PH and supports the ideas that high TRV may predispose to PA dilation.

Limitations

There are several limitations of our study. In diagnostic-accuracy assessment, our study population consisted of a variety of abnormal control patients, because of the lack of CTA scans of healthy volunteers. However, these controls were not primarily diagnosed with pulmonary pathology. Another limitation relates to a lack of relevant longitudinal studies. Our results present the hemodynamic profile of SCD patients at a particular point in time, and thus it is unclear how PA size correlates with the course of SCD over a long-term period. Likewise, it is also unclear at what stage of SCD these measurements may be most useful as either diagnostic or predictive. In future work, it would be useful to characterize comorbid organ dysfunction/failure or other aspects of SCD linked to both its progression and its manifestation. Another important factor to consider in future studies of PH and PA structure in SCD patients is the severity of anemia. Further, since the CT, echocardiogram, and catheterization were not performed at the exact same time (within 1 day for echocardiogram, within 3 days for catheterization), other factors such as hydration status, cardiovascular medications, and opiate administration were not controlled and could theoretically have introduced certain unpredictable variables. However, many of these variables should have been applied in a random fashion, distributed across all groups.

Only 20 patients were entered on the SCD arm; therefore, some patient selection bias may have been introduced, which might make these results valid only for similar patients, such as those sick enough to require CTA, echocardiogram, and catheterization during an acute crisis. There was no racial matching between these patients and the normal controls because of the lack of sufficient normal cases with CTA. Although the sample population

was limited, note that the power of the study was greater than 90%.

Error analysis between manual and CAD measurements of PA showed in quantitative fashion that our segmentation method resulted in accurate measurements of the maximum distension in the PT and PB. PT and PB sizes were shown to differ significantly between cases and controls, with these measurements consistent with findings of previous studies.^{16,21,34} This, along with the semi-automatic method of segmentation and computation itself, demonstrates the reproducibility of our results.

Closing remarks

Our study shows the potential of CTA with quantitative image analysis in the diagnosis of PH secondary to SCD and in the understanding of hemodynamics related to vascular remodeling. In particular, we report several important correlations between PA diameter from CTA image analysis and hemodynamics relevant to PH, such as cardiac output, which is an increasingly recognized contributor to the development and unfavorable outcome of PH in SCD. Consistent with those in other studies, results in this study reflect characteristics common to many forms of PH. On the other hand, because we investigated patients with PH secondary to SCD, it is reasonable to assume that the etiology of PH in our population may in fact be hemodynamically different from that of PH secondary to other diseases. Overall, the complex relationships between the presence of anemia, hemodynamic markers of PH, vessel morphology, and the resulting poor outcomes in these patients all point to an increasing need for alternative, noninvasive tools to aid in the diagnosis and disease management of this population. Cone beam CT (CBCT) can be acquired in many standard angiography catheterization labs and may provide another outlet for similar conclusions, since CBCT evaluations of PA can be acquired simultaneously during heart catheterization. Moreover, CTA or CBCT could potentially be used in screening for the onset of PH in SCD.

This study used semiautomated measurements from CTA that have previously shown to be consistent and reproducible, but such image-based technology is not currently available for wide clinical use. However, we found that there is very high correlation between manual and semiautomated measurements ($r = 0.88-0.93$), which indicates that manual measurements of PA could be used to assess PH.² Although our study was conducted on CTA data, one of its main findings is that PA diameter is an indicator of PH. This conclusion opens the avenue to investigate image-based tools for PH screening, pref-

erably on nonirradiating modalities, such as ultrasound imaging.

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