indicating that subphenotype assignment also has strong prognostic relevance in children with ARF but not PARDS.

Recent investigations in adults with ARF without ARDS also support the existence of two subphenotypes with characteristics similar to those seen in patients with ARDS, again distinguishable by inflammatory biomarkers and by clinical outcomes (5, 8). Thus, these two subphenotypes share overlap across the adult and pediatric ARF spectra, offering a rationale for innovative trial enrollment strategies across ages.

Our findings emphasize the challenge of syndromic definitions such as PARDS in specific, and ARF in general, which struggle to identify and characterize complex pathophysiologic processes that culminate from multiple inciting diagnoses. Our data suggest that the complex inflammatory pathways and inflammatory-related subphenotypes associated with PARDS (3, 9) are also involved in children with ARF, and recent data suggest that they may also be observed in other critically ill children (10).

In conclusion, these data suggest that parsimonious model subphenotype assignment can enable robust prognostic enrichment compared with prior risk stratification schema. Earlier identification of high-risk subphenotypes, particularly in pediatric patients, could result in earlier escalation of care in patients at greater risk for complex course.

After validation, these data may impact future clinical trial design, including the expansion of subphenotype identification to the broader pediatric ARF cohort. ■

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Right Ventricular Response to Acute Hypoxia among Healthy Humans

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To the Editor:

Pulmonary arterial (PA) pressures and right ventricular (RV) afterload increase in response to hypoxia (1). Limited data are available that describe RV adaptations to acute hypoxia and the associated increases in afterload, occurring in response to clinical scenarios such as infections, pulmonary embolism, and hypoxia associated with high-altitude exposure (2).

RV pressure-volume analysis by means of conductance catheterization is a gold-standard method of characterizing RV function using metrics of contractility, lusitropy, energetics, and ventricular-arterial coupling (3). The primary objective of this single-center prospective study (ClinicalTrials.gov ID NCT 05272514) was to characterize RV performance in response to acute progressive hypoxia.

The results of this study have been previously reported in an unpublished abstract (4).

Healthy adults free of cardiovascular, hematologic, and pulmonary disease underwent hemodynamic assessment. Individuals residing at ⩾2,500 m (8,000 ft) for three or more consecutive nights within 30 days of testing were excluded (2). Written informed consent was obtained. The study was approved by the institutional review board of the University of Colorado Anschutz Medical Campus and overseen by an independent data safety and monitoring board. Participants underwent baseline evaluation with Swan-Ganz catheterization. Thereafter, they were randomized 1:1 to undergo hypoxic testing with Swan-Ganz catheterization versus a conductance catheter inserted into the right ventricle. Oxygen saturation (Sa_{O_2}) and blood pressure were monitored with a radial arterial catheter. Oxygen uptake was continuously recorded (Vyntus, Vyaire Medical) for calculation of direct Fick cardiac output (5, 6). For participants randomized to testing with a conductance catheter, the Swan-Ganz catheter was replaced by a 7F high-fidelity conductance catheter (CD Leycom). Insertion and calibration were performed according to previous protocols (5, 6). Single-beat estimation was used to determine end-systolic elastance, effective arterial elastance, and ventricular-arterial coupling (5, 6). Participants were exposed to staged reductions in $F_{I_{O_2}}$ at 0.21, 0.17, 0.15, and 0.12 every 8–10 minutes by means of an open circuit with Douglas bag reservoirs. Hemodynamic parameters were recorded in the final minute of each stage of hypoxia. Data are reported as mean ± SD or median (and interquartile range) unless otherwise specified.

Ten participants completed the study (34 ± 10 years; three women; body mass index, 24.3 ± 2.7 kg/m^2). Baseline hemodynamics among all participants demonstrated a right atrial pressure of 3 mm Hg (1, 3), a mean PA pressure of 12 mm Hg (9, 15), PA wedge

Table 1. Invasive Hemodynamic Response to Acute Hypoxia Derived from Pulmonary Arterial and Conductance Catheterization

	$F_{I_{O_2}} = 0.21$	$F_{I_{O_2}} = 0.17$	$F_{I_{O_2}} = 0.15$	$F_{I_{O_2}} = 0.12$	*P* Value
Swan-Ganz catheter (*N* = 5)					
HR, bpm	53 (50, 62)	54 (52, 62)	55 (53, 72)	63 (53, 73)	0.06
RAP, mm Hg	3 (1, 3)	3 (1, 3)	3 (1, 3)	1 (0, 2]*†‡	<0.01
PAS, mm Hg	18 (14, 20)	17 (15, 22)	20 (16, 22)*	25 (25, 31)*†‡	<0.01
PAD, mm Hg	8 (4, 10)	9 (8, 11)	9 (8, 11)	9 (7, 13)	0.25
mPAP, mm Hg	12 (7, 13)	12 (11, 13)	13 (13, 13)	14 (13, 19)*	0.01
PAWP, mm Hg	6 (6, 6)	6 (6, 7)	5 (4, 10)	6 (3, 10)	0.92
PA Sat, %	71 (69, 72)	64 (64, 67)	64 (58, 64)*	53 (49, 61)*†‡	<0.01
Arterial Sat, %	96 (94, 97)	93 (89, 96)	86 (83, 90)*†	76 (71, 81)*†‡	<0.01
SV, ml/beat	125 (101, 151)	107 (80, 184)	114 (97, 174)	147 (124, 166)	0.69
Qc, L/min	7.4 (6.1, 8.7)	6.2 (5.8, 8.8)	8.2 (6.8, 9.2)	9.7 (7.2, 11.3)	0.40
PVR, WU	0.9 (0.5, 1.0)	1.0 (0.8, 1.1)	1.1 (0.5, 1.1)	1.0 (1.0, 1.1)	0.10
Conductance catheter (*N* = 5)					
RV contractility					
$dPdt_{max}$, mm Hg/s	268 (240, 271)	283 (257, 312)	315 (296, 340)	448 (342, 476)*†‡	<0.01
ESP, mm Hg	17 (17, 18)	19 (18, 21)	23 (19, 23)	27 (23, 28)*†	<0.01
PRSW, mm Hg	7 (6, 13)	14 (12, 14)	14 (14, 19)	20 (11, 26)*	0.02
RV lusitropy					
$dPdt_{min}$, mm Hg/s	−208 (−219, −195)	−243 (−260, −225)	−275 (−297, −232)	−331 (−396, −295)*†‡	<0.01
RV energetics					
SW, mm Hg · ml	1,750 (1,489, 2,697)	2,777 (2,697, 2,900)	3,503 (3,229, 3,536)	3,578 (2,558, 5,440)*	0.03
Ventricular-arterial coupling					
E_{ES}, mm Hg/ml	0.21 (0.19, 0.25)	0.19 (0.18, 0.25)	0.23 (0.18, 0.25)	0.24 (0.20, 0.25)	0.54
E_A, mm Hg/ml	0.16 (0.15, 0.17)	0.13 (0.11, 0.15)	0.14 (0.12, 0.15)	0.18 (0.14, 0.18)†‡	0.02
E_{ES}/E_A, units	1.51 (1.35, 1.73)	1.50 (1.42, 1.62)	1.43 (1.32, 1.84)	1.35 (1.33, 1.41)	0.47

Definition of abbreviations: Arterial Sat = arterial oxygen saturation; bpm=beats per minute; $dPdt_{max}$ = maximum rate of pressure change; $dPdt_{min}$ = minimum rate of pressure change; E_A = effective arterial elastance; E_{ES} = end-systolic elastance; E_{ES}/E_A = ventricular-arterial coupling; ESP = end-systolic pressure; HR = heart rate; mPAP = mean pulmonary arterial pressure; PA Sat = pulmonary arterial oxygen saturation; PAD = pulmonary arterial diastolic; PAS = pulmonary arterial systolic; PAWP = pulmonary artery wedge pressure; PRSW = preload recruitable stroke work; PVR = pulmonary vascular resistance; Qc = cardiac output; RAP = right atrial pressure; RV = right ventricular; SV = stroke volume; SW = stroke work; WU = Wood units.
Data are presented as median (interquartile range).
*$P < 0.05$ for comparison with an $F_{I_{O_2}}$ of 0.21.
†$P < 0.05$ for comparison with an $F_{I_{O_2}}$ of 0.17.
‡$P < 0.05$ for comparison with an $F_{I_{O_2}}$ of 0.15.

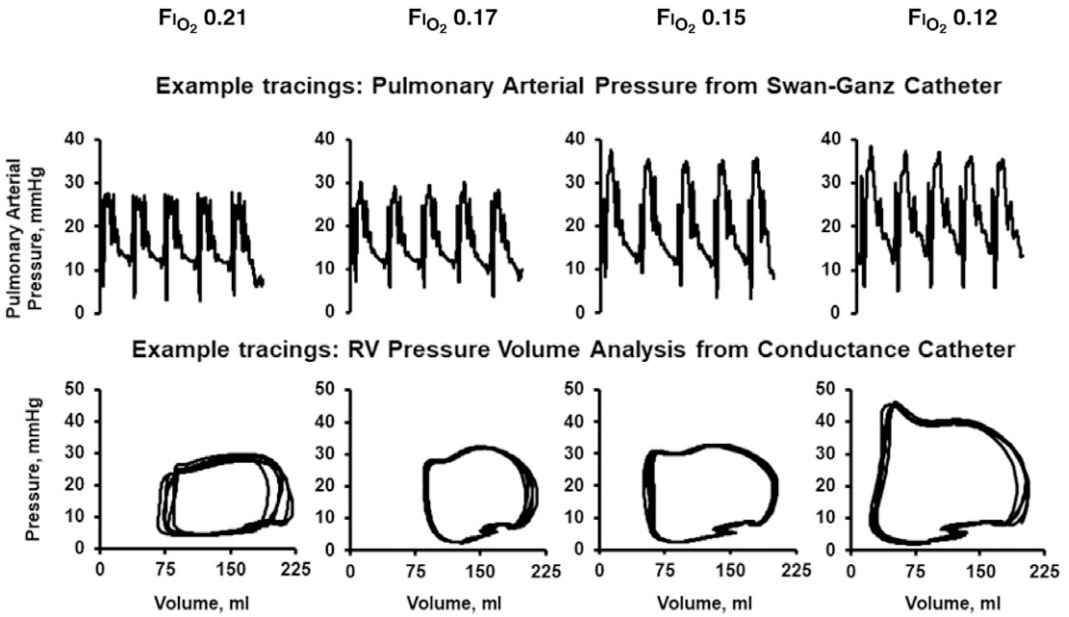

Figure 1. Example hemodynamic tracings demonstrating the response to acute hypoxia. RV = right ventricular.

pressure of 6 mm Hg (6, 6), and direct Fick cardiac output of 8.8 L/min (7.2, 9.2). Sa_{O_2} at a FI_{O_2} of 0.21 was 95% (94, 96) and decreased to 71% (70, 77) at a FI_{O_2} of 0.12. Hemodynamics during progressive reduction in FI_{O_2} are demonstrated in Table 1. Example hemodynamic tracings are demonstrated in Figure 1. Progressive hypoxia led to a modest increase in PA pressure from 12 (7, 13) to 14 (13, 19) mm Hg among participants evaluated with a Swan-Ganz catheter ($N = 5$) and in RV afterload from 0.16 (0.15, 0.17) to 0.18 (0.14, 0.18) mm Hg/ml among those evaluated with a conductance catheter ($N = 5$). Cardiac output increased because of modest increases in heart rate and stroke volume. Acute hypoxia increased metrics of RV contractility, lusitropy, and myocardial energetics, and RV ventricular-arterial coupling was preserved.

The primary findings from this study are as follows: *1*) Mean PA pressure increased by ~17% in response to an acute reduction in FI_{O_2} from 0.21 to 0.12; *2*) despite the associated increase in RV afterload, there were concomitant increases in RV contractility, lusitropy, and energetics; consequently, *3*) RV ventricular-arterial coupling was preserved.

Limited studies have characterized RV performance in response to hypoxia. Operation Everest II demonstrated that RV afterload increased during a gradual transition from sea level (760 mm Hg) to a simulated Everest summit (240 mm Hg), and RV function, as determined by right atrial pressure, was preserved (1). Among healthy individuals ($N = 35$), echocardiographic assessment of RV systolic pressure increased after 150 minutes of exposure to an FI_{O_2} of 0.11 (FI_{O_2}, 0.21 vs. 0.11: 17.4 ± 3.3 mm Hg vs. 24.9 ± 4.8 mm Hg) with an associated reduction in tricuspid annular plane systolic excursion (FI_{O_2}, 0.21 vs. 0.11: 21 ± 1.4 mm vs. 17 ± 1.5 mm; $P < 0.05$), suggesting decreased RV systolic function in response to increased afterload (7).

This study assessed RV performance using complementary gold-standard methodologies of PA hemodynamics and pressure-volume analysis. Noninvasive methodologies are inherently limited when characterizing PA and RV hemodynamics. Isolated metrics from invasive PA assessments such as right atrial pressure do not adequately characterize RV contractility, lusitropy, energetics, or ventricular-arterial coupling. Thus, data provided in this analysis provide unique insight into RV performance in response to acute increases in afterload, such as that which occurs during acute hypoxia.

These findings can be contextualized among pressure-volume analyses of RV function in other clinical states. For example, metrics of contractility and myocardial energetics during supine rest at FI_{O_2} of 0.15 and 0.12 were similar to values among healthy individuals performing normoxic submaximal exercise (5). Contractility, as assessed by maximum rate of pressure change, was similar, at a FI_{O_2} of 0.12, to that observed in an animal model of acute intermediate–high-risk pulmonary embolism, though in contrast to the pulmonary embolism model, healthy individuals at a FI_{O_2} of 0.12 demonstrated lower afterload and preserved ventricular-arterial coupling (8). Finally, preload recruitable stroke work increased in response to progressive hypoxia to levels comparable with those in patients with PA hypertension associated with systemic sclerosis (9).

Limitations to our study include the small sample size, albeit a size similar to that in prior invasive studies (1). The majority of the participants were males, and gender-specific differences in RV function could not be determined. Second, we evaluated RV performance in response to acute (<1 h) hypoxia among healthy participants and did not include an analysis of RV changes that occur during prolonged exposure to hypoxia.

In conclusion, the healthy RV demonstrates significant contractile reserve such that ventricular-arterial coupling is preserved during acute hypoxia. Additional studies are necessary to characterize longitudinal changes in RV function during chronic hypoxia as well as RV response to hypoxia among individuals with cardiopulmonary disease (2, 10). ■

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