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Title: A novel method for evaluating regional RV function in the adult congenital heart with low-dose CT and SQUEEZ processing

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Abstract:

25 *Background:* Measuring local RV function in adult congenital heart disease (ACHD)
with echocardiography or MRI is challenging because of the complex geometry and
existing pacing devices. Visual assessment of ventricular function via low-dose cardiac
CT has been recently performed. This pilot study assessed whether low-dose 4D cine
30 CT combined with automatic measurement of regional shortening could quantify right-
ventricular function in ACHD patients.

Methods: Seven patients with Tetralogy of Fallot either contraindicated for MRI or
assessed for coronary artery disease and seven non-congenital patients were imaged
with ECG gated cardiac CT utilizing a 320-detector row scanner. Right ventricular global
35 function and regional shortening were quantified.

Results: Non-congenital patients were imaged with 2.9 ± 2.1 mSv and 395 ± 359 HU
blood-myocardium contrast. The ACHD patients were imaged with 2.1 ± 1.3 mSv and
726 \pm 296 HU contrast. Right ventricles of the ACHD patients had higher end-diastolic
40 volume (297 ± 107 mL vs 123 ± 34 mL, $p = 0.001$), lower ejection fraction (32.0 ± 4.9 %
vs 45.0 ± 6.0 %, $p = 0.001$), and higher dyskinetic fraction (10.9 ± 3.7 % vs 2.6 ± 2.8 %,
 $p < 0.001$) relative to the non-congenital controls.

Conclusions: In this initial pilot study, right ventricular global and regional systolic
45 function were measured using low-dose cine CT with SQUEEZ quantification in non-
congenital patients as well as ACHD patients with Tetralogy of Fallot. Unique regional
features of RV dyskinesia were identified in the ACHD patients which could yield a more
precise quantification of RV function.

50 **Keywords:** Adult congenital heart disease; cardiac computed tomography; systolic
function

1. Introduction:

55 Adults with congenital heart disease (ACHD) represent a growing portion of adult
cardiovascular care [1]. As these patients enter adulthood, there is a clinical need for
routine assessment of cardiac function to identify the onset of ventricular dysfunction,
tailor medical therapy, and recommend interventions such as valve replacement or
cardiac resynchronization therapy [2].

60 Assessment of ventricular function in ACHD patients with echocardiography is
challenging due to the complex anatomy, often large ventricle sizes, and poor
echocardiographic windows after surgery [3]. Cardiac magnetic resonance imaging
(MRI) has been the gold-standard as a non-ionizing imaging method to provide accurate
65 volumetric information. However, cardiac MRI may be contraindicated in patients with
pacemakers or implantable cardioverter-defibrillators [3].

Traditionally, cardiac computed tomography (CT) has been limited by the radiation
exposure and limited temporal resolution when compared to echocardiography and
70 cardiac MRI [3]. However, a low radiation dose, contrast-enhanced, retrospectively-
gated cardiac CT protocol with a median radiation dose of less than 1 mSv was recently
shown to successfully evaluate global biventricular systolic function in 30 consecutive
patients [4]. Furthermore, quantification of regional shortening via 4D cine CT using
SQUEEZ [5] analysis has recently been shown to distinguish normal and infarcted
75 regions of the left ventricle and has been validated using MRI tagging [5,6].

In this pilot study, we combine these two advances in CT imaging to demonstrate the
ability of low radiation dose retrospectively-gated CT combined with SQUEEZ
processing to quantify the distribution of right ventricular regional shortening in normal
80 adults as well as ACHD patients with Tetralogy of Fallot. This approach provides both
global and regional measures of systolic function that can be utilized to monitor function
longitudinally as well as quantify response to treatment.

85 2. Methods:

Patients were scanned under an IRB approved protocol at the National Institutes of
Health. The study protocol conformed to the ethical guidelines of the 1975 Declaration
of Helsinki. All subjects provided written informed consent to participate. The ACHD
90 patients were at least 18 years old with congenital heart disease and were clinically
referred for contrast-enhanced cardiac CT. Exclusion criteria were pregnancy or renal
dysfunction, estimated glomerular filtration rate less than 30 mL/min/1.73 m² [7].
Patients were not excluded for weight, heart rate, or heart rhythm.

95 *Patient Population:*

Overall, 14 patients were included in the study. Relevant demographics are shown in **Table 1**. Seven patients without congenital heart disease were imaged due to concern of coronary artery disease and served as anatomical controls (#1-7). The imaging showed no or non-obstructive epicardial coronary artery disease and had sufficient myocardium-blood contrast (> 170 HU) in the RV for SQUEEZ quantification of function. Seven ACHD patients with repaired Tetralogy of Fallot were included in the study (#8-14). The imaging and clinical condition of each patient are outlined below.

Patient	ACHD	Sex	Age	Height (cm)	Weight (kg)	BMI (kg/m ²)	Dose (mSv)	X-Ray Energy (kV)	Maximum Tube Current (mA)	RV Blood-Myocardium Contrast (Hu)	CNR
1	N	F	59	163	58.2	22.0	1.22	100	250	690.3	21.2
2	N	M	47	173	97.7	32.8	6.13	100	790	174.2	4.4
3	N	F	52	163	88.6	33.5	0.75	80	140	1089.2	21.7
4	N	F	67	157	99.7	40.4	3.18	100	820	265.2	6.7
5	N	F	61	152	54.6	23.5	1.52	100	330	215.9	6.3
6	N	F	53	157	77.3	31.2	5.27	100	690	181.4	5.5
7	N	F	51	152	59.1	25.4	2.78	100	420	149.6	5.0
			<i>55.7 ± 6.9</i>	<i>159.6 ± 7.4</i>	<i>76.4 ± 19.4</i>	<i>29.8 ± 6.5</i>	<i>3.0 ± 2.1</i>	<i>97.1 ± 7.6</i>	<i>491 ± 274</i>	<i>395.1 ± 358.9</i>	<i>10.1 ± 7.8</i>
8	Y	M	33	174	84.0	27.7	3.24	80	220	710.8	14.5
9	Y	F	49	171	86.4	29.5	2.41	80	320	528.3	10.2
10	Y	F	48	170	63.2	21.8	0.60	80	90	1272.3	37.9
11	Y	M	45	175	109.1	35.5	3.38	100	240	358.3	9.0
12	Y	M	41	180	94.3	29.1	3.11	100	470	685.6	18.7
13	Y	F	43	156	66.4	27.3	1.07	80	450	608.9	12.9
14	Y	F	56	169	73.2	25.6	0.70	80	250	915.0	20.4
			<i>45.0 ± 7.2</i>	<i>170.7 ± 7.5</i>	<i>82.4 ± 16.2</i>	<i>28.1 ± 4.2</i>	<i>2.1 ± 1.2</i>	<i>85.7 ± 9.8</i>	<i>291 ± 134</i>	<i>725.6 ± 295.5</i>	<i>17.7 ± 9.8</i>

Table 1: Demographic patient information, radiation Dose and RV Enhancement for non-congenital patients (1-7) and ACHD patients (8-14) The average and standard deviation are shown beneath each group. CNR: Contrast-to-noise ratio

All congenital patients had a prior transannular patch repair.

Patient 8 had prior pulmonary valve replacement, and biventricular pacemaker implantation and was referred for biventricular assessment of systolic function.

Patient 9 was referred for biventricular assessment for evaluation of right-ventricular end-diastolic size and systolic function in consideration for pulmonary valve replacement. A breast tissue expander after mastectomy was a contraindication for MRI.

Patient 10 had prior pulmonary valve replacement, residual ventricular septal defect repair, and dual-chamber ICD implantation and was referred for biventricular assessment of systolic function.

Patient 11 had a re-do repair with reconstructed right ventricular outflow tract, recurrent VSD patch repair, and was referred for coronary artery and biventricular functional assessment.

Patient 12 was referred for coronary artery and biventricular functional assessment. The scan spanned two RR-intervals due to arrhythmia.

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Patient 13 had a prior bioprosthetic pulmonary valve replacement and was referred for coronary artery and biventricular functional assessment.

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Patient 14 had a prior percutaneous closure of an atrial septal defect, dual-chamber ICD placement, aortic aneurysm, and was referred for biventricular functional assessment.

Image Acquisition:

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Patients underwent cardiac CT scans with axial imaging using a second-generation, 320 × 0.5-mm detector row CT unit (Aquilion ONE ViSION Edition; Toshiba Medical Systems, Otawara, Japan) with a gantry rotation time of 275 msec and acquisition over the entire cardiac cycle. End-diastolic and end-systolic frames for non-congenital and adult congenital patients are shown in **Figure 1A-B**.

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For the non-congenital patients as well as congenital patients referred for assessment of coronary arteries, a dose modulation protocol was performed to allow for assessment of the coronary arteries and systolic function. The maximum tube current is reported in **Table 1**. ACHD patients 8-10 and 14 underwent a low radiation dose retrospectively-gated cardiac CT scan to assess biventricular function. Patients 11-13 were referred for simultaneous function and coronary imaging and therefore received higher radiation dose imaging at end-diastole to visualize the coronary arteries.

150

Tube potential and tube current were determined by automatic exposure control (^{SURE}Exposure3D, Toshiba Medical Systems) on the basis of the X-ray attenuation on scout images and reconstruction kernel [8]. Images were reconstructed with a 512 × 512 matrix, 0.5 mm thick sections, and 0.25-mm increments using kernel FC03, iterative reconstruction AIDR3D in “standard” mode. (Toshiba Medical Systems, Otawara, Japan).

155

Right ventricular (RV) blood-myocardium contrast was quantified via the difference in Hounsfield units between the myocardial blood pool and septal myocardium measured in axial image. Contrast-to-noise ratio (CNR) was estimated by dividing the contrast by the standard deviation of the intensity observed in the anterior chest wall.

160

Regional Quantification of Function:

Regional shortening quantification was carried out using custom software in MATLAB. The basic steps were 1) Short-axis reformatting of the 4-dimensional dataset, 2) ITK-SNAP region-growing segmentation of the RV blood volume at each timeframe, 3) Calculation of RV volumes and ejection fraction, 4) SQUEEZ analysis [9] of 3D RV blood volumes with the “template” volume being the earliest timeframe after the QRS and the “target” volumes being the subsequent time points.

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SQUEEZ analysis estimates the deformation of small triangular faces on the endocardial surface over time. For a patch v , the SQUEEZ value is:

$$SQUEEZ(v, t) = \sqrt{\frac{A(v, t)}{A(v, 0)}}$$

175 where t is the frame in the cine CT images and A is the area of the patch v . This yields a length measure of shortening. We report regional shortening from CT (RS_{CT}) as $RS_{CT} = (SQUEEZ - 1)$.

180 **Figure 1C-E** illustrates the how regional shortening is quantified. For visualization, the size of the triangles has been increased and three example triangles are shown depicting normal, hypokinetic, and dyskinetic motion. From the global volume curve, the minimum volume time frame is labeled end-systole and RS_{CT} values from this timeframe are obtained. Dyskinetic segments have end-systolic RS_{CT} values > 0 .

185 The heterogeneity of regional shortening was visualized by rendering end-systolic regional shortening values on the RV blood volume surface.

190 Dyskinesia was quantified via the percentage of the endocardial surface with end-systolic lengthening (RS_{CT} at end-systole > 0). The mean and standard deviation of end-systolic RS_{CT} across the endocardial surface are reported in **Table 2**.

Statistical Analysis:

195 Differences in patient demographics, x-ray dose, image quality, and right ventricular function were evaluated via a two-way, unpaired, Student's t-test with a significance level of $p < 0.05$.

3. Results:

Patient Population:

200 The ACHD patients were significantly ($p = 0.03$) taller (170.7 ± 7.5 cm) than the normal controls (159.6 ± 7.4 cm) but there were no significant differences in age ($p = 0.06$), weight ($p = 0.52$), or BMI ($p = 0.48$).

Imaging Radiation Dose and RV Contrast Enhancement:

205 The radiation dose and RV myocardium – blood contrast for all patients are shown in **Table 1**. The radiation doses were comparable ($p = 0.37$) but the ACHD patients had images with higher contrast ($p < 0.01$) and CNR ($p = 0.04$). This can be attributed to imaging being timed earlier to ensure RV enhancement and a lower tube potential in some of the ACHD patients compared to imaging of non-congenital patients which targeted enhancement of the left ventricle and coronary arteries.

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End-diastolic and end-systolic images for 3 non-congenital patients and 3 ACHD patients are shown in **Figure 1A** and **1B**. Biventricular function is displayed via conventional echocardiographic views in supplementary movies 1 and 3.

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Global Function Quantification:

Segmentation of the right ventricle throughout the cardiac cycle allowed for volumetric quantification, measurement of end-diastolic and end-systolic volume, stroke volume, and estimation of ejection fraction. The results are shown in **Table 2**. Volume over time curves for patient 1 and patient 8 are shown in **Figure 2A-B**.

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The right ventricles of the ACHD patients were larger ($p = 0.001$), had higher end-systolic ($p = 0.001$) and stroke volumes ($p = 0.009$), and had lower global function ($p = 0.001$) compared to the non-congenital controls.

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Patient	ACHD	EDV (mL)	ESV (mL)	SV (mL)	EF (%)	RS _{CT}	Dyskinesia (%)
1	N	112.3	52.6	59.7	51.4	-0.17 ± 0.07	0.3
2	N	185.9	99.6	86.3	45.2	-0.15 ± 0.08	4.7
3	N	139.4	78.6	60.7	43.6	-0.12 ± 0.09	2.3
4	N	104.4	66.8	37.7	36.1	-0.15 ± 0.14	7.7
5	N	76.4	43.9	32.5	42.6	-0.17 ± 0.05	0.4
6	N	121.0	70.0	51.0	42.2	-0.14 ± 0.08	3.0
7	N	121.5	56.0	65.5	53.9	-0.19 ± 0.06	0.0
		<i>123.0 ± 33.8</i>	<i>66.8 ± 18.6</i>	<i>56.2 ± 18.1</i>	<i>45.0 ± 6.0</i>	<i>-0.16 ± 0.02</i>	<i>2.6 ± 2.8</i>
8	Y	364.1	247.3	116.8	32.1	-0.13 ± 0.10	12.8
9	Y	399.6	252.2	147.4	31.1	-0.03 ± 0.19	9.9
10	Y	321.6	230.2	91.4	24.1	-0.07 ± 0.08	11.9
11	Y	406.7	286.1	120.6	27.4	-0.09 ± 0.08	16.5
12	Y	121.7	76.1	45.6	36.8	-0.13 ± 0.11	11.2
13	Y	256.6	148.2	108.4	36.1	-0.12 ± 0.07	4.5
14	Y	206.1	131.5	74.6	36.2	-0.12 ± 0.09	9.4
		<i>296.6 ± 106.7</i>	<i>195.9 ± 77.4</i>	<i>100.7 ± 33.4</i>	<i>32.0 ± 4.9</i>	<i>-0.10 ± 0.04</i>	<i>10.9 ± 3.7</i>

Table 2: Global and regional measures of RV function. EDV: end-diastolic volume, ESV: end-systolic volume, SV: stroke volume, EF: ejection fraction, RS_{CT}: mean end-systolic regional shortening, Dyskinesia: percentage of the RV with end-systolic RS_{CT} > 0.

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Regional Assessment of Function:

Regional shortening was measured in all patients throughout the RV endocardial surface. Four views of the end-systolic shortening are shown in **Figure 2C** and **2D** for patient 1 (non-congenital) and 8 (ACHD), respectively. 360 degree rotations of the end-systolic shortening are available in supplementary movies 2 and 4. The distribution of end-systolic regional shortening values are shown in **Figure 2E** and **2F**. The dyskinetic fraction of the RV endocardial surface (RS_{CT} > 0 at end-systole) was quantified and is reported in **Table 2**. Congenital patients demonstrated both lower average RS_{CT} across the RV ($p = 0.003$) as well as increased dyskinetic endocardial area ($p < 0.001$).

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4. Discussion:

In this pilot study, we demonstrated that four-dimensional estimation of global and regional right ventricular systolic function with cine cardiac CT can be obtained in

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patients with complex ventricular geometry, including those with congenital heart disease and implanted metal such as pacemakers and defibrillators. In our study, we observed the expected global RV dilation and reduced ejection fraction in the Tetralogy of Fallot patients. In addition, we were able to perform regional shortening analysis
250 which demonstrated large regions of right ventricular dyskinesia in the Tetralogy of Fallot patients relative to the non-congenital controls. While the extent of the dyskinetic regions varied between the individual patients, they were primarily located within the right ventricular outflow tract related to the transannular patch.

255 Despite global RV dilation, decreased ejection fraction, and regions of dyskinesia, we observed regions with preserved shortening in the Tetralogy of Fallot patients (Figure 3D). This suggests our method can identify not only the regions of dyskinesia but also regions of preserved functional myocardium. This regional assessment could provide important information for early detection of dysfunction, treatment planning, and
260 treatment response beyond what is observed from global measures such as end-diastolic volume or ejection fraction.

Recent work has shown that cardiac MRI measurements of global left and right ventricular systolic function can improve risk stratification for ventricular arrhythmias and death in adult Tetralogy of Fallot patients [10]. These risk models may identify those
265 high-risk Tetralogy of Fallot patients who would benefit from an implantable cardioverter-defibrillator [10–12]. The method described in this report provides these global measurements as well as regional measures of systolic function and is not contraindicated in patients with pacemaker or defibrillators. Future research is needed
270 to assess whether the quantity of dyskinetic segments is a marker for increased risk for future ventricular failure or ventricular arrhythmias.

In our study, four of the 7 ACHD patients had contraindications for MRI due to implanted metal (pacemaker, defibrillator, and breast tissue expander). With decreasing radiation
275 doses and a population increasingly requiring pacemaker or defibrillator implantation, Cardiac CT may become more widely used in the ACHD population [4,13]. The presence of cardiac devices did not limit the ability of our approach with cardiac CT to provide global or regional quantification. As a result, our approach of low radiation dose CT imaging combined with global and regional quantification of systolic function has the
280 potential to enable longitudinal assessment of patients including pre- and post-surgical intervention.

Our study incorporated two distinct populations which required very different scanning parameters: one without congenital heart disease being evaluated for coronary artery
285 disease and one with congenital heart disease being evaluated for ventricular shape and function. For the assessment of coronary artery disease, higher resolution imaging requires higher tube currents for improved image quality to visualize sub-millimeter stenoses and coronary plaques. For adult congenital heart disease, the clinical assessment of cardiac size and function is obtained with lower radiation dose technique

290 with low mA and low kVp techniques to minimize radiation exposure. Nevertheless, the
SQUEEZ algorithm for quantification of regional function was able to provide robust
results over a wide variety of tube currents in these two populations.

295 Our mean radiation dose in ACHD patients (2.1 mSv) was higher than the 0.94 mSv
median dose previously reported [4]. This was due to two several factors. First, patients
had higher BMIs ($28.1 \pm 4.2 \text{ kg/m}^2$) than the prior study cohort ($24.2 \pm 4.3 \text{ kg/m}^2$).
Furthermore, patient 8 and 1 had arrhythmias during imaging which led to multiple heart
300 beat acquisition and further increased the radiation dose. Finally, 3 of the 7 ACHD
patients were referred for assessment of biventricular function as well as coronary
artery evaluation. This led to utilizing dose modulation with increased mA at end-
diastole for appropriate visualization of the coronary arteries, which also contributed to
the increased radiation dose.

305 **Limitations:**

This work is a pilot study with retrospective analysis of fourteen patients. The CT-
derived measures of systolic function were not validated against a gold standard. Most
of the ACHD patients in our study had contraindications to MRI and the remaining
ACHD patients and normal controls were referred for non-invasive assessment of
310 coronary artery disease. Due to the retrospective design, neither MRIs nor volumetric
echocardiography were obtained in these subjects. However, previous work has shown
close agreement between CT and MR-derived measures of function in ACHD patients.
Yamasaki et al demonstrated high correlation between RV measures ($r= 0.71 - 0.96$),
slight overestimation of RV EDV (17.1 mL), ESV (12.9 mL), and SV (4.2 mL), slight
315 underestimation of RV EF (2.6%), and lower variability in CT-derived measures relative
to MRI [7].

The study utilized a 320-detector row CT scanner which is available at a limited number
of centers. Although the quantification could be performed on scans obtained with fewer
320 detector rows, it could introduce stitching artifacts and result in higher radiation dose.

5. Conclusions:

325 In this initial pilot study, global and regional systolic function were successfully
measured using low radiation dose 4D cine CT with SQUEEZ quantification in non-
congenital patients as well as ACHD patients with Tetralogy of Fallot.

330 **6. Funding sources:**

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335

7. Conflicts of interest:

340 The National Heart, Lung, and Blood Institute of the National Institutes of Health has an institutional research agreement with Toshiba Medical Systems.

8. Acknowledgments:

345 None

9. Figure Captions:

350 **Figure 1: A)** End-diastolic and end-systolic four-chamber images of 3 non-congenital patients. WL/WW: 200/2000. **B)** End-diastolic and end-systolic four-chamber images of 3 ACHD patients (8-10) with Tetralogy of Fallot. WL/WW: 200/2000 **C-E)** Quantification of regional shortening. SQUEEZ analysis provides estimates of regional deformation of small triangular patches along the endocardial surface. The size of the patches have
355 been exaggerated for visualization in panel **C**. Three exemplary regions showing normal contraction (green), hypokinesia (orange), and dyskinesia (blue) are shown. The global volume curve (panel **D**) is used to estimate end-systole. This point is used to identify end-systolic regional shortening values from the time curves in panel **E**.

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Figure 2: Global and regional quantification of non-congenital and ACHD patient. Global RV function measured from the change in blood pool volume for patient 1 (panel **A**) and patient 8 (panel **B**) illustrate the extent of dilation in an ACHD patient. Four views of the regional shortening at end-systole are shown for patient 1 (panel **C**) and patient 8 (panel **D**). The areas of dyskinesia (end-systolic dilation, shown in yellow) occur along the anterior free wall and outflow tract. Histogram analysis (panel **E** and **F**) illustrates the distribution of regional shortening, limitations with measurement of an average value, and the percentage of RV endocardium that is dyskinetic.

370 10. Supplementary Files:

Supplemental Movie 1: Standard echocardiographic views from the 4DCT data of patient 1 (non-congenital). WL/WW: 200/2000

375 *Supplemental Movie 2:* 3D rendering of end-systolic RS_{CT} for patient 1 (non-congenital). The figure illustrates near uniform shortening throughout the right ventricle.

Supplemental Movie 3: Standard echocardiographic views from the 4DCT data of patient 8 (ACHD - repaired tetralogy of Fallot). WL/WW: 200/2000

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Supplemental Movie 4: 3D rendering of end-systolic RS_{CT} for patient 8 (ACHD - repaired tetralogy of Fallot). The rendering illustrates substantial regional heterogeneity as well as large regions of dyskinesia (yellow).

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