Exercise-dependent changes in ventricular–arterial coupling and aortopulmonary collateral flow in Fontan patients: a real-time CMR study

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Aims
Inefficient ventricular–arterial (V–A) coupling has been described in Fontan patients and may result in adverse haemodynamics. A varying amount of aortopulmonary collateral (APC) flow is also frequently present that increases volume load of the single ventricle. The aim of the study was to assess changes in V–A coupling and APC flow during exercise CMR.

Methods and results
Eighteen Fontan patients (age 24 ± 3 years) and 14 controls (age 23 ± 4 years) underwent exercise CMR using a cycle ergometer. Ventricular volumetry and flow measurements in the ascending aorta (AAO), inferior (IVC), and superior (SVC) vena cava were assessed using real-time sequences during stepwise increases in work load. Measures of systemic arterial elastance (Ea), ventricular elastance (Ees), and V–A coupling (Ea/Ees) were assessed. APC flow was quantified as AAO - (SVC + IVC). Ea remained unchanged during all levels of exercise in both groups (P = 0.39 and P = 0.11). Ees increased in both groups (P = 0.001 and P < 0.001) with exercise but was lower in the Fontan group (P = 0.04). V–A coupling was impaired in Fontan patients at baseline (P = 0.04). Despite improvement during exercise (P = 0.002) V–A coupling remained impaired compared with controls (P = 0.001). Absolute APC flow in Fontan patients did not change during exercise even at maximum work load (P = 0.98).

Conclusions
Inefficient V–A coupling was already present at rest in Fontan patients and aggravated during exercise due to a limited increase in ventricular contractility which demonstrates the importance of a limited functional reserve of the single ventricle. APC flow remained unchanged suggesting no further increase in volume load during exercise.

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Introduction

Single ventricle dysfunction represents a major risk factor for early and late failure of the Fontan circulation.\(^1\)\(^2\) Ventricular functional impairment can develop from myocardial damage that may occur throughout the staged surgical palliation, chronic ventricular underfilling, myocardial remodelling, and persistent abnormal haemodynamic loading conditions. An increase in volume load arises from atrioventricular valve regurgitation but can also result from a substantial degree of blood flow through aortopulmonary collateral (APC) arteries. In addition, higher ventricular afterload seems to be related to increased systemic vascular resistance and elevated aortic vascular stiffness following surgical reconstruction of the aorta.\(^3\)\(^4\)

Considering the prognostic relevance of single ventricular dysfunction in Fontan patients, reliable quantification of ventricular performance remains crucial in this population. However, routine assessment of ventricular function usually includes ejection fraction as a parameter of global pump function that is affected by altered ventricular loading conditions. Since strain imaging yield less load-dependent indices of ventricular function, echocardiographic speckle, and CMR tissue tracking techniques have been increasingly used to analyse single ventricle function. The concept of ventricular–arterial (V–A) coupling has further advantages as it overcomes some of the restrictions related to the load-sensitivity of myocardial function and provides a more differentiated analysis of cardiovascular mechanical efficiency.

Cardiovascular magnetic resonance (CMR) imaging has emerged as an essential and prognostically relevant non-invasive imaging modality in Fontan patients. However, haemodynamics routinely quantified by CMR are assessed under resting conditions. As a consequence, early detection of subclinical single ventricular dysfunction and pathologic blood flow patterns that potentially occur with exercise may be missed. The combination of CMR compatible ergometer systems and real-time (RT) sequences represent an innovative approach that allows quantification of ventricular function and blood flow during exercise and thereby also to study V–A coupling and APC flow during physical stress.\(^5\)\(^6\)

By using a CMR compatible cycle ergometer, we evaluated single ventricle function in patients with total cavopulmonary connection (TCPC) and a group of healthy volunteers. The aim of our study was (i) to assess changes and differences in V–A coupling between Fontan patients and healthy controls during exercise, (ii) to study changes of APC flow with exercise in the Fontan group, and (iii) to detect differences in these measures in patients with right and left ventricular morphology.

Methods

Study population

Fontan patients older than 12 years of age who were scheduled for a CMR examination as part of their routine clinical assessment at our
department as well as healthy volunteers > 18 years of age were asked to participate in the exercise CMR study. The chosen age limit resulted from the physical and cognitive skills that are required to perform such an ambitious exercise protocol. Candidates were excluded in case of general contraindications for CMR (pacemaker, ferromagnetic artificial implants, etc.). Fontan patients were also excluded: (i) if there was evidence of flow through a patent tunnel fenestration, (ii) if single ventricle function appeared to be considerably impaired on echocardiography (ejection fraction <40%), (iii) if there were any obstructions within the Fontan pathway, pulmonary arteries, or aortic arch diagnosed by echocardiography or CMR, (iv) if atrioventricular or (neo-) aortic valve regurgitation was more than moderate, (v) any significant history of tachy- or bradyarrhythmia was present, and/or (vi) if patients were in impaired clinical condition (NYHA functional class IV) that was unable to complete the exercise protocol.

Demographic data were retrospectively obtained from hospital medical records including date of birth, gender, anatomic diagnoses, age at, and type of each surgical and interventional procedure. New York Heart Association (NYHA) classification was used to grade the severity of functional limitations. The study protocol was registered and approved by the local ethics committee. Written informed consent for participation of the study was obtained from all patients or parents of the patients and all healthy volunteers.

Assessment of ventricular–arterial coupling
The framework of V–A coupling defines the ventricle and arterial system as two elastic chambers. While several concepts have been applied to assess V–A coupling non-invasively, the most frequently used method is that described by Chen et al. which adheres to the following formulas:

1. Effective arterial elastance $E_a$

\[ E_a = \frac{ESP}{SV}, \]

where ESP is the end-systolic pressure and SV is the ventricular stroke volume.

It has been shown that $0.9 \times$ systolic blood pressure (SBP) closely approximates ESP. Accordingly, using CMR assessment of SV and oscillometric measurement of SBP, $E_a$ can be calculated non-invasively,

\[ E_a = \frac{0.9 \times SBP}{SV}, \]

where SBP is the systolic non-invasive blood pressure (BP) and SV is the ventricular stroke volume.

2. Ventricular end-systolic elastance $E_{es}$

\[ E_{es} = \frac{ESP}{ESV}, \]

where ESP is the end-systolic pressure and ESV is the ventricular end-systolic volume.

By using $0.9 \times$ SBP as the ESP, formula (2) becomes

\[ E_{es} = \frac{0.9 \times SBP}{ESV} \]

3. V–A coupling ratio

\[ \frac{E_a}{E_{es}} = \frac{ESV}{SV} \]

It has been demonstrated that normal ventricular functional adaptation to afterload is associated with maintenance of an $E_a/E_{es}$ ratio $\sim 0.5$, allowing for flow output at a minimal amount of energy cost, and optimal V–A coupling ratio occurs when the ventricle and arterial system have equal elastances.

CMR exercise protocol
All patients and healthy volunteers underwent cycle CMR exercise in supine position (Figure 1). A standardized protocol was used in an identical
fashion for both groups: after a first measurement at rest (baseline),
the protocol included a stepwise increase of 15 W intensity every
5 min with the definite goal to achieve the 60 W level in both patients
and controls. The pre-determined pedal-rate was 40–50 turn per min.
RT volumetric and flow measurements were performed during con-
tinuous exercise at steady-state without any hold in cycling or breath-
ing. Assessment of ventricular volumes and blood flows were
achieved after 60 s to guarantee measurements at a steady-state at
each intensity level. A prerequisite for a reliable image analysis was
only minor motion artefacts. Patients were asked to keep body move-
ment during cycling to a minimum as possible by holding the handgrips
at the site of the ergometer. The decision to choose 15 W steps was
based on our first experiences with the exercise protocol that had to
include both volumetric and flow measurements within a limited time
interval without exceeding a total exercise time that may not be suc-
cessfully completed by the group of Fontan patients.

Non-invasive systolic and diastolic arm-cuff BP, transcutaneous oxygen
saturation (tcSO₂), and heart rate (HR) were continuously measured
throughout all exercise levels using a standard CMR compatible monitor-
ing system (Invivo precess, Invivo Corporation, Orlando, FL, USA).

Statistical analysis
All continuous variables were tested for normality using the D’Agostino-
Pearson omnibus test and are presented as mean with standard deviation
(SD). Comparisons within one group at different exercise levels were
conducted by a repeated measures (RM) analysis of variance (ANOVA).
The Greenhouse–Geisser adjustment was used to correct for violations
of sphericity. Bonferroni correction for multiple testing was applied.
Group comparisons (Fontan vs. healthy controls and Fontan subgroups)
were determined by Student’s t-test or Mann–Whitney U test as appro-
priate, testing parameters at different levels of exercise separately.
Analysis was performed using SPSS GraphPad statistical software package
(San Diego, CA, USA) and SPSS statistical software package (version
25.0; IBM, Armonk, NY, USA).

Results
Patient characteristics and clinical
findings
Eighteen TCPC patients (mean age 24 ± 3 years, 4 females) and 14
healthy controls (mean age 23 ± 4 years, 5 females, \( P = 0.17 \)) under-
went a complete exercise study using a recumbent CMR-compatible
cycle ergometer (Lode, Groningen, The Netherlands, Table 1). Systemic RV morphology was present in 6 patients while 12 patients
had a systemic LV. The majority of Fontan patients was in NYHA
class I (39%) and II (50%). Two of originally 22 examined Fontan
patients had to be excluded from final analysis because the 60 W level
was not achieved, one patient was excluded due to higher grade aor-
tic valve regurgitation and another patient was excluded because of
imaging artefacts.

RT CMR and image analysis
For detailed description of the used RT cine and 2D phase contrast flow
sequences as well as further image analysis please see Supplementary
data online, Data S1. In brief, ventricular volumes were assessed in short-
axis orientation and were calculated after the endocardial borders were
traced manually (Figure 2A). Flow measurements were performed in the
ascending aorta (AAO), inferior (IVC), and superior (SVC) caval vein
(Figure 2B). APC flow was quantified using the systemic flow estimator:
AAO – (SVC + IVC).

Figure 2 (A) Example of a short-axis cine real-time cine image at baseline and during 60 W exercise level of a Fontan patient. The endocardial bor-
der (red) was traced manually at end-diastole and end-systole. The position of the diaphragm was evaluated to guarantee measurements at the same
time point during breathing cycles. (B) Image analysis of 2D real-time phase contrast measurements in the ascending aorta, inferior caval vein (IVC,
TCPC tunnel), and the superior caval vein (SVC). Note that blood flow was obtained over a time period of 10 s in each vessel. Regions of interest
were drawn encircling the dedicated vessel and propagated manually across all frames.
Clinical and haemodynamic changes assessed by CMR
During exercise, Fontan patients showed a blunted increase in HR (63 ± 9 to 96 ± 10/min, vs. 68 ± 6 to 117 ± 16/min, P < 0.0001) compared with healthy controls (Figure 3 and see Supplementary data online, Data S2). The tcSO2 levels in the Fontan group were lower than in the control group but remained >90% during exercise in all patients. BPs were not significantly different between the groups and increased during exercise in both groups (P < 0.001, respectively).

Ventricular size and function
Indexed end-diastolic ventricular volumes (EDVi) were comparable between Fontan patients and healthy controls at rest and throughout all stages of exercise (Figure 3 and see Supplementary data online, Data S2). Stroke volumes increased in both groups up to the 45 W level and were not different between patients and controls. At baseline, EF was significantly lower in the Fontan group (60 ± 7% vs. 66 ± 5%, P = 0.02) and increased with higher exercise levels to a maximum at 45 W and then decreased at 60 W. In contrast, a continuous rise in EF throughout all exercise levels was noted in healthy controls at 60 W: 65 ± 8% vs. 76 ± 5%, P < 0.0001.

Parameters of Ea, Ees, and V–A coupling
Ea did not differ between the two groups at rest (0.69 ± 0.29 vs. 0.64 ± 0.24 mmHg/mL/m², P = 0.68) and remained unchanged during exercise (at 60 W: 0.74 ± 0.34 vs. 0.66 ± 0.28 mmHg/mL/m², P = 0.78). Ees was not different at rest (P = 0.45), increased significantly during exercise in both groups (P = 0.001 and P < 0.0001) but was significantly lower at 60 W in Fontan patients (1.09 ± 0.46 to 1.50 ± 0.81 vs. 1.21 ± 0.39 to 2.20 ± 0.99 mmHg/mL/m², P = 0.04, Figure 4 and see Supplementary data online, Data S2). V–A coupling was impaired in Fontan patients at baseline (0.67 ± 0.20 vs. 0.53 ± 0.12, P = 0.04). Despite improvement during exercise (P = 0.002), V–A coupling was still impaired in Fontan patients compared with controls (at 60 W: 0.54 ± 0.20 vs. 0.32 ± 0.09, P = 0.001).

Changes in blood flow and APC flow in Fontan patients
With exercise, flow in the IVC (TCPC tunnel) increased from 1.8 ± 0.4 to 3.6 ± 0.7 L/min/m² at 60 W (P < 0.001) and SVC flow increased from 0.7 ± 0.2 to 1.0 ± 0.4 L/min/m² at 60 W (P = 0.01). Absolute APC flow in Fontan patients did not change during exercise even at maximum work load (from 0.7 ± 0.5 to 0.8 ± 0.7 L/min/m² at 60 W, P = 0.98) while APC flow as a percentage of flow in the AAO even decreased significantly (from baseline 21 ± 13% to 13 ± 12% at 60 W, P = 0.036, Figure 5). The Qp/Qs ratio subsequently dropped from 1.3 ± 0.2 to 1.1 ± 0.2 (P = 0.012).

Relevance of systemic right or left ventricle morphology
Patients with a systemic LV (n = 12) were compared with a group of patients with a systemic RV (n = 6, Figure 6). The single RV group was slightly younger (mean age 21.3 ± 3.1 vs. 23.5 ± 3.8 years, P = 0.25) but no differences were observed with other demographic and clinical data. No difference in Ea was noted between the two groups both at rest and with exercise. Ea was already reduced in patients with a systemic RV (0.8 ± 0.3 vs. 1.2 ± 0.5 mmHg/mL/m², P = 0.028) at rest and did not increase significantly with exercise to 0.9 ± 0.3 mmHg/mL/m² (P = 0.20) whereas in patients with LV morphology, Ea increased to 1.8 ± 0.8 mmHg/mL/m² (P < 0.001). While Ea/Ees was not different between the two groups at rest (P = 0.06), it only improved with exercise in the LV group (from 0.6 ± 0.1 to 0.5 ± 0.2, P = 0.001) while the change in the RV group was not significant (from 0.8 ± 0.2 to 0.7 ± 0.2, P = 0.30) resulting in favourable V–A coupling at 45 W (P = 0.48) and 60 W (P = 0.03) intensity in the LV group.

Discussion
Our study demonstrated that compared with healthy controls, Fontan patients show an inefficient V–A coupling already at rest that is further aggravated during exercise primarily caused by a limited increase in ventricular contractility. Systemic arterial elastance as a composite parameter of ventricular afterload was comparable between Fontan patients and healthy controls and remained unchanged during all levels of exercise. Furthermore, the absolute amount of APC flow did not increase during exercise in the Fontan group. These results demonstrate the importance of an altered intrinsic functional reserve of the single ventricle but no further increase in afterload or pre-load through APCs during exercise. Thus, altered single ventricle mechanical efficiency represents an important feature in Fontan patients that can be unmasked with exercise CMR and may potentially enable earlier diagnosis of impaired haemodynamics.

### Table I Demographic data of the study population

| Variable                        | Fontan | Healthy controls | P-value |
|---------------------------------|--------|------------------|---------|
| Number, n                       | 18     | 14               |         |
| Male/female                     | 14/4   | 9/5              | 0.33    |
| Weight (kg)                     | 71 ± 14| 70 ± 10          | 0.71    |
| BSA (m²)                        | 1.85 ± 0.20 | 1.83 ± 0.18 | 0.73    |
| Diagnoses, n (%)                |        |                  |         |
| TA                              | 7 (39) |                  |         |
| DILV                            | 4 (22) |                  |         |
| HLHS                            | 3 (17) |                  |         |
| ccTGA                           | 2 (11) |                  |         |
| DORV                            | 2 (11) |                  |         |
| Single ventricle morphology     |        |                  |         |
| Right, n                        | 6      |                  |         |
| Left, n                         | 12     |                  |         |
| Age at study (years)            | 23 ± 4 | 24 ± 3           | 0.71    |
| Age at TCPC (years)             | 3.5 ± 1.3 |            |         |
| NYHA I/II/III/IV, n             | 7/9/2/0|                  |         |
| Cardiac medication, n (%)       |        |                  |         |
| ACE inhibitors                  | 4 (22) |                  |         |
| Beta-blocker                    | 2 (11) |                  |         |

Data are presented as mean with 1 SD. ccTGA, congenital corrected transposition of the great arteries; DILV, double inlet left ventricle; DORV, double outlet right ventricle; HLHS, hypoplastic left heart syndrome; n, number; NYHA, New York Heart Association functional class; TA, tricuspid atresia; TCPC, total cavopulmonary connection.
Fontan haemodynamics, ventricular function, and V–A coupling

Role of exercise haemodynamics in Fontan patients using CMR

Advanced imaging techniques may help to detect unfavourable haemodynamic changes in Fontan patients in order to assess the cardiovascular response to physical exercise. An approach using both the advantages of superior image quality of CMR combined with exercise stress is the installation of a compatible ergometer system that allows continuous exercise performance during RT acquisition. By using this technique in Fontan patients, previous studies delivered important insight into the physiological mechanisms leading to rise in pulmonary blood flow such as respiration, peripheral muscle pump function, and low pulmonary vascular resistance (PVR) providing adequate ventricular filling and cardiac output. Another group reported a significant relationship between power loss within the circulation and clinical exercise capacity.

Exercise-induced changes in V–A coupling

Our study adds important findings on this topic, showing that inefficient V–A coupling is already present at rest in Fontan patients that will further aggravate during exercise. This response seems to be

Figure 3 Graph showing routine haemodynamic parameters of heart rate (HR), indexed ventricular end-diastolic volume (EDVi), end-systolic volume (ESVi), stroke volume (SVi), ejection fraction (EF), and cardiac index (CI) both in Fontan patients (orange) and healthy controls (blue). Data are displayed as mean with 1 SD. An asterisk (*) indicates a significant change from the baseline intensity. A dagger (†) indicates a significant difference between the two groups (see Supplementary data online, Data S2). Comparisons within one group at different exercise levels were conducted by a repeated measures analysis of variance (RM ANOVA).
In contrast, Schmitt and colleagues assessed V–A coupling in Fontan patients during dobutamine stress and found an improvement in Ees but also a simultaneous rise in Ea and a subseuent unchanged coupling ratio.11 In an invasive conductance catheter technique, another group reported improved V–A coupling with dobutamine that was mediated by a distinct increase in Ees while Ea also raised significantly.14,15 The inotropic and lusitropic effect of dobutamine as well as its impact on systemic and PVR may explain the different results of the mentioned studies.16 Importantly, physical exercise occurring with the cycle ergometer activates muscle pump function of the legs and thereby creates a different physiological hemodynamic situation than dobutamine with a greater extent of blood returning from the lower extremities.

It should be noted that the V–A coupling ratios in our Fontan group were within the normal Ea/Ees ranges (<1) that are reported in a healthy adult population. Nevertheless, compared with the healthy subjects in our study, inefficient V–A coupling was present at rest but showed a significant improvement under exercise, however, not to the same extent as observed in healthy controls. Accordingly, V–A uncoupling with an Ea/Ees ratio >1 was found only in two patients at baseline conditions in our study population that might be explained by the fact that the majority of patients included was primarily NYHA classes I and II. In fact, Godfrey et al.12 included 195 Fontan patients and found V–A coupling ratios from 0.34 to 4.18 (median 0.88). Importantly, higher V–A coupling ratios were also associated with adverse outcomes. Whether detection of unfavourable changes in V–A coupling during exercise may also improve prediction of adverse outcome remains speculative although results from dobutamine stress studies suggest such an impact.17

Single ventricle volumes and global pump function
Analysis of ventricular function and ventricular–vascular interactions in Fontan patients should take into account that adequate ventricular filling relies on preserved ventricular diastolic compliance and low PVR.4 In a previous exercise CMR study, van de Bruaene et al.5 combined invasive pressure and RT cine volumetric measurements to assess exercise performance in Fontan patients. In their population, end-diastolic and stroke volumes as well EF started to decrease already at moderate exercise levels whereas end-systolic volumes remained unchanged. The authors attributed these findings to a combination of reduced pre-load and impaired contractility relative to systemic afterload. Different changes were observed in our Fontan group that showed unchanged end-diastolic but increased stroke volumes with exercise. Again, this might be attributable to a Fontan study cohort in overall good clinical condition presenting with preserved ventricular contractility, good anastomotic function, well-developed pulmonary arteries and low PVR allowing for sufficient ventricular filling with exercise but might also be related to an impaired HR response. However, other than in healthy controls, the rise in ventricular Ees was blunted which demonstrates reduced contractile reserve, a phenomenon that might be related to adverse intrinsic myocardial remodelling characterized by focal and diffuse fibrotic changes. Considering the prognostic relevance of strain measurements in single ventricle patients,18 the application of CMR tissue tracking to quantify strain and strain rate during exercise would give further insights into myocardial performance. This technique,

mediated primarily by a limited increase in ventricular elastance Ees rather than by an abnormal elevation in vascular afterload Ea. The results elucidate the emerging role of adverse ventricular–vascular interactions as a contributing mechanism for deterioration in single ventricle function and impaired response to exercise that support the importance of studying the Fontan circulation under exercise conditions.

In accordance with our findings, two groups recently demonstrated normal afterload but reduced contractile function and impaired V–A coupling within a larger number of adult Fontan patients under resting conditions.11,12 Other studies, however, reported an elevation in Ea following Fontan surgery causing an contractility-afterload mismatch and reduced mechanical efficiency.4

Figure 4 Diagrams displaying changes in systemic arterial elastance Ea, ventricular elastance Ees, and the ratio of ventricular–arterial coupling Ea/Ees in Fontan patients (orange) vs. healthy controls (blue). Data are displayed as mean with 1 SD. An asterisk (*) indicates a significant change from the baseline intensity. A dagger (†) indicates a significant difference between the two groups (see Supplementary data online, Data S2). Comparisons within one group at different exercise levels were conducted by a repeated measures analysis of variance (RM ANOVA).
Figure 5 Changes in aortopulmonary collateral (APC) flow in Fontan patients during exercise. The absolute amount of APC flow remained unchanged ($P = 0.98$), while APC flow as a percentage of flow in the ascending aorta (AAO) decreased significantly ($P = 0.036$). Data are displayed as mean with 1 SD. Comparisons at different exercise levels were conducted by a repeated measures analysis of variance (RM ANOVA).

Figure 6 Diagrams showing the key variables $E_a$, $E_{es}$, and $E_a/E_{es}$ in the subgroups of Fontan patients with a morphological left (LV, $n = 12$, purple) or a morphologic right systemic single ventricle (RV, $n = 6$, green). Data are presented as mean with 1 SD. An asterisk (*) indicates a significant change from the baseline intensity. A dagger (†) indicates a significant difference between the two groups (see Supplementary data online, Data S3). Comparisons within one group at different exercise levels were conducted by a repeated measures analysis of variance (RM ANOVA). BL, baseline; $E_a$, systemic arterial elastance; $E_{es}$, ventricular elastance; $E_a/E_{es}$, ratio of ventricular–arterial coupling; $W$, watt intensity.
more distinct decrease in single ventricle morphology with exercise as observed in patients with a systemic LV. Accordingly, intrinsic myocardial dysfunction seems to play a major factor for an inefficient V–A coupling in patients with a systemic RV. APC flow remained unchanged suggesting no further increase in volume load during exercise.

Imade, however, relies on adequate spatial and temporal resolution to ensure correct endocardial tracking but was not sufficient with the used RT sequence in our study.

**Inadequate heart rate response in Fontan patients**

Compared with controls, the capability to increase cardiac output was markedly reduced in our Fontan group, which was primarily caused by a reduced increase in HR rather than by inappropriate variations in stroke volumes during exercise. The phenomenon of chronotropic incompetence has been well described in the Fontan population and has been linked with adverse outcome. Interestingly, a recent exercise CMR study identified reduced pre-load as the potential mechanism for the blunted HR response rather than sinoatrial dysfunction. Ruijsink and colleagues further demonstrated that selective HR inhibition with ivabradine led to an increase in stroke volume, cardiac output, and V–A coupling while another study observed a more distinct decrease in single ventricle mechanical and energetic efficiency with higher HRs. Accordingly, modulation of HR may therefore represent a potential target to improve exercise Fontan haemodynamics.

**Changes in blood flow and relevance of APC flow**

As already demonstrated in previous studies, blood flow in the Fontan pathways (i.e. TCPC tunnel and SVC) increased gradually with exercise. Despite these significant changes, the absolute amount of APC flow did not change during exercise while its percentage of ascending aortic flow even decreased significantly. This demonstrates that APC induced volume load of the single ventricle remains stable even with higher exercise levels and may therefore not explain reduced exercise capacity in these patients. Our findings are in accordance with a previous study that also quantified APC flow under submaximal exercise. In contrast, Schmitt et al. used pharmacological stress and noted a significant increase in APC flow under inotropic stimulation with dobutamine. As already mentioned, these differences might be explained by a modulation of PVR under dobutamine stress.

**Impact of single ventricle morphology**

Right ventricular morphology seems to be associated with suboptimal adaption to haemodynamic stress and obviously results in adverse clinical outcomes. Although limited by the small number of patients in this subgroup analysis, our results suggest impaired V–A coupling as another important feature in patients with a systemic RV that is further unmasked with exercise. Importantly, Ea did not differ between the two groups although the RV group included three HLHS patients with a history of aortic arch reconstruction that has been suspected to increase aortic stiffness. In contrast, impaired Ees was already present at rest and did not improve substantially with exercise as observed in patients with a systemic LV. Accordingly, intrinsic myocardial dysfunction seems to play a major factor for an inefficient V–A coupling in patients with a systemic RV. These results are in accordance with the findings of a recent CMR study that reported lower circumferential shortening and increased fibre stress in systemic RV. Other data, however, suggest that RV systolic intrinsic function is increased compared with LV patients, potentially as a compensatory response to match with higher Ea and maintain V–A coupling.

While higher APC flow in patients with HLHS has been reported, volume load through APCs was similar, both at rest and under exercise, within the two groups. Therefore, APC flow seems to be less relevant in the evolution of larger ventricular volumes in the RV group.

**Study limitations**

Measurements of peak oxygen uptake using cardiopulmonary exercise testing (CPET) was not part of the study protocol but would enable to investigate the relationship between reduced exercise performance and V–A coupling parameters. As a consequence, the chosen CMR exercise levels were not adapted to the results of the CPET study, nor were the levels gender- or age-matched. Due to imaging artefacts that occurred with body movement at higher exercise levels, analysis of both flow and cine images was challenging (in patients more than in healthy controls) and, according to our experience, may not be reliable at a workload exceeding 60 W. Accordingly, although the participants were asked to exercise until subjective maximal exertion, the presented values at highest cycle intensity may not represent individual maximal exercise capacity. The limited temporal and spatial resolution of the used RT CMR sequences may also affect our results. The simplified non-invasive method to quantify Ea and Ees seems error-prone considering that parameters such as Ea may also be affected by HR. Furthermore, although frequently used in literature, the Ea/Ees ratio as used in our study may not contain itself superior haemodynamic information compared with EF but enables differentiation between the components of afterload and intrinsic myocardial dysfunction.

**Conclusions**

Inefficient V–A coupling was already present at rest in Fontan patients and aggravated during exercise due to a limited increase in ventricular contractility which demonstrates the importance of a limited functional reserve of the single ventricle. APC flow remained unchanged suggesting no further increase in volume load during exercise.

**Supplementary data**

Supplementary data are available at European Heart Journal - Cardiovascular Imaging online.

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