ARTICLE IN PRESS

International Journal of Cardiology xxx (xxxx) xxx

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Stress imaging in patients with a Fontan circulation: A systematic review

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ARTICLE INFO

Keywords:
Fontan circulation
Single ventricle
Cardiac magnetic resonance
Echocardiography
Cardiac stress imaging
Dobutamine

ABSTRACT

Introduction: The aims of this study were to provide an overview of the cardiac stress response in Fontan patients and of the use, safety and clinical value of stress imaging in Fontan patients.
Methods: Studies evaluating cardiac function using stress imaging in Fontan patients published up until 12 December 2021 were included in this review.
Results: From 1603 potential studies, 32 studies met the inclusion criteria. In total, stress imaging tests of 728 Fontan patients were included. Cardiac function was most often measured using physical stress (61%), all other studies used dobutamine-induced stress.
Stroke volume (SV) increased in most studies (71%), mean SV at rest ranged from 27 mL/m^2 to 60 mL/m^2 versus 27 mL/m^2 to 101 mL/m^2 during stress, and increased with an average of 4%. Ejection fraction increased in almost all studies, whereas both end-systolic volume and end-diastolic volume decreased during stress. Higher heart rates were obtained with physical stress (82–180) compared to dobutamine induced stress (73–128). Compared to controls, increases in heartrate and SV were lower and end-diastolic volume decreased abnormally in 75% of reporting studies. No major adverse events were reported. Poorer cardiac stress response was related to decreased exercise capacity and higher risk for long-term (adverse) outcomes in Fontan patients.
Discussion: Cardiac stress response in Fontan patients differs from healthy subjects, reflected by lower increases in heart rate, diminished preload and decreased cardiac output, especially during higher levels of exercise. Stress imaging is safe, however the added clinical value needs to be investigated in more detail.

1. Introduction

The Fontan procedure is considered when biventricular repair is not possible in patients with complex congenital heart diseases with hypoplasia of one of the ventricles [1]. This procedure includes a series of operations performed at different ages, eventually creating a total cavopulmonary connection (TCPC). During the Fontan procedure the inferior caval vein (IVC) and the superior caval vein (SVC) are connected directly to the pulmonary arteries, bypassing the subpulmonary ventricle, and thereby leading to separation of the two circulations [1]. As a result of this procedure patients have an increased life expectancy and a higher quality of life [2]. Nevertheless, limited exercise capacity and deterioration of cardiac function remain long-term problems in these patients [3]. Patients with a Fontan circulation struggle to adequately increase venous return, evidently resulting in a decreased ventricular preload and the inability to properly increase stroke volume with exercise [4]. The following abnormalities during stress testing in patients who underwent the Fontan procedure can be expected: decreased exercise capacity, lowered blood oxygenation and respiratory response and abnormal cardiac output responses [5]. Stress imaging can be used to investigate the abnormal stress response of the heart in patients with a Fontan circulation, which is important as exercise intolerance is often a first sign in gradual deterioration of the Fontan circulation [1,3]. Understanding the abnormal stress response of Fontan patients could possibly help devise new strategies for treatment. Several methods of cardiac stress imaging exist, using both pharmacological induced stress and physical exercise. These methods can be combined with different imaging techniques [6]. Experience regarding stress imaging is growing, as more studies have been using this relatively new technique and have investigated the added clinical value in patients

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https://doi.org/10.1016/j.ijcard.2023.131192
Received 11 June 2023; Accepted 14 July 2023
Available online 19 July 2023

with a Fontan circulation. A systematic overview of stress imaging in patients with a Fontan circulation is lacking in current literature. The aims of this study were to provide an overview of a) the cardiac response to stress in Fontan patients, b) the use of different techniques and protocols for performing stress imaging in Fontan patients, c) the safety of cardiac stress imaging in patients with a Fontan circulation and d) the clinical/prognostic value of stress imaging in Fontan patients.

2. Methods

2.1. Search strategy

On December 12, 2021, a search was conducted by the medical library staff of the Erasmus MC. The search terms consisted of the following search terms: a) Fontan procedure or variant names, b) Congenital anomalies and syndromes that form an indication for treatment with the Fontan procedure, c) Different types of stress imaging. The full search can be found in supplemental data 1. The search was limited to original research papers published in English. A time restriction for publication dates was not used. The following databases were searched: Embase, Medline ALL, web of science core collection, Cochrane Central Register of Controlled Trials and Google Scholar.

2.2. Inclusion and exclusion criteria

Based on the aim of this study, the following inclusion criteria were defined:

a) the study included patients with a Fontan circulation.

b) patients were subjected to any form of stress imaging.

c) results of the Fontan group were separated from potential other results.

Exclusion criteria were:

a) the study is a review, letter or conference abstract.

2.3. Data extraction

After full-text screening, both reviewers extracted the following data: Study characteristics: author, year of publication, study design, study size (of patient group and of control group if applicable), type of controls, imaging modality used, type of stress, dose of dobutamine, patient's position during stress imaging. Patient characteristics: sex, age, age at Fontan completion, Fontan type, cardiac defect, dominant ventricle. Outcome measurements: stroke volume, ejection fraction, heart rate, end diastolic volume index, end systolic volume index and aortic flow, all at rest and during stress, and adverse events.

2.4. Quality assessment

The STROBE quality assessment was used for all included articles, articles were assessed independently by two reviewers. Disagreements in quality assessment were discussed with a third reviewer (LES) until a consensus was met.

2.5. Statistical analysis

Due to the large heterogeneity of the included studies and data, a meta-analysis was not performed and the results are presented as descriptive data. Continuous data is presented as mean +/− standard deviation (SD) or as median, dependent on the data given in the included studies. Categorical variables are presented as counts and percentages. Weighted pooling was conducted to calculate change in cardiac outcomes during rest versus stress. The highest intensity (highest dose for pharmacologically induced stress or highest wattage/Heartrate for physical stress) presented in the included study was used to calculate stress effects on each cardiac outcome.

3. Results

3.1. Literature search results

A total of 1603 studies were identified using the search as listed in supplement 1. After screening based on title and abstract, a total of 1415 articles were excluded, reasons for exclusion are shown in Fig. 1. After screening the remaining 188 articles on full text, another 156 articles were excluded, resulting in a total of 32 included articles in this systematic review. Quality assessment showed overall good to moderate scores, lowest score was 70% (supplemental table 2).

3.2. Patient characteristics

Supplemental table 3 shows a summary of all patient characteristics. In total, data was collected of 728 Fontan patients who completed a study protocol involving any form of stress imaging. Mean age of the patient groups ranged from 3,9 to 28 years. Most studied patients had a dominant left ventricle (43,4%). The most reported indications for a Fontan circulation were tricuspid atresia (n = 133), hypoplastic left heart syndrome (n = 88), and double inlet left ventricle (n = 55). Most used surgical repairs were the extracardiac connection (n = 304) and the intra-atrial lateral tunnel (n = 212), and atriopulmonary connection (n = 18) (these patients were not excluded as they were part of a larger cohort).

3.3. Imaging techniques

Cardiac magnetic resonance (CMR) was used in 23 of the included studies to perform stress imaging [3,7–28], of which one combined this technique with cardiac cauterization [22], 7 studies used echocardiography [29–35]. Two studies used gated radionuclide angiography. Most studies used physical stress during or right before cardiac imaging (61%) [7–11,13,15–18,23,24,27,30,31,34–37]. The majority of the studies that performed physical stress, used a bicycle ergometer with the patient exercising in supine position [7–9,11,15–18,23,24,27,35,37]. Thirteen studies performed cardiac stress imaging using pharmacological induced stress, all using dobutamine [12,14,19–22,25,26,28,29,32,33,38]. Details regarding study characteristics and used imaging techniques can be found in Table 1.

3.4. Cardiac stress response

Cardiac stress response was summarized in Fig. 2 and supplemental table 4. In total, twenty-four studies reported stroke volume (SV) at rest and during stress [7–12,14–24,26,28–30,32–34]. In 17 of these studies, an increase in SV was found during stress [7,8,10–12,14–18,22,23,26,29,30,33,34]. Romeih et al. showed no change in SV between rest and stress [21]. The other six studies measured a decrease in SV during stress, compared to rest [9,19,20,24,28,32]. Mean SV at rest ranged from 26.7 mL/m^2 to 60 mL/m^2 versus 27.1 mL/m^2 to 101.1 mL/m^2 during stress, mean (weighted) increase in SV was 4%. Cortes et al. found that stroke volume in Fontan patients initially increased, and then decreased back to resting levels during exercise (on average after 6 min of exercise) [30]. Sixteen studies measured change in ejection fraction (EF), of which 15 showed an increase during stress [7,9,14,16,19–22,24–26,28,29,36–38]. The study by Claessen et al. was the only to report a decrease in EF during stress (−4,6%) [9]. EF ranged from 38% to 65% at rest and from 40% to 72% during stress, mean weighted increase was 13%.

Heart rate (HR) at rest and during stress was reported in 26 studies, all showed an increase in HR (increase between 6 and 95 bpm) [7,9–11,13,14,16–22,24,26–35,37,38]. Fifteen studies reported indexed end diastolic volume (EDVi) and end systolic volume (ESVi) during rest and stress [7–9,14,19–24,26,28,29,32,38]. Ten of these studies showed a decrease in EDVi (mean decrease 9%) during stress and eleven studies

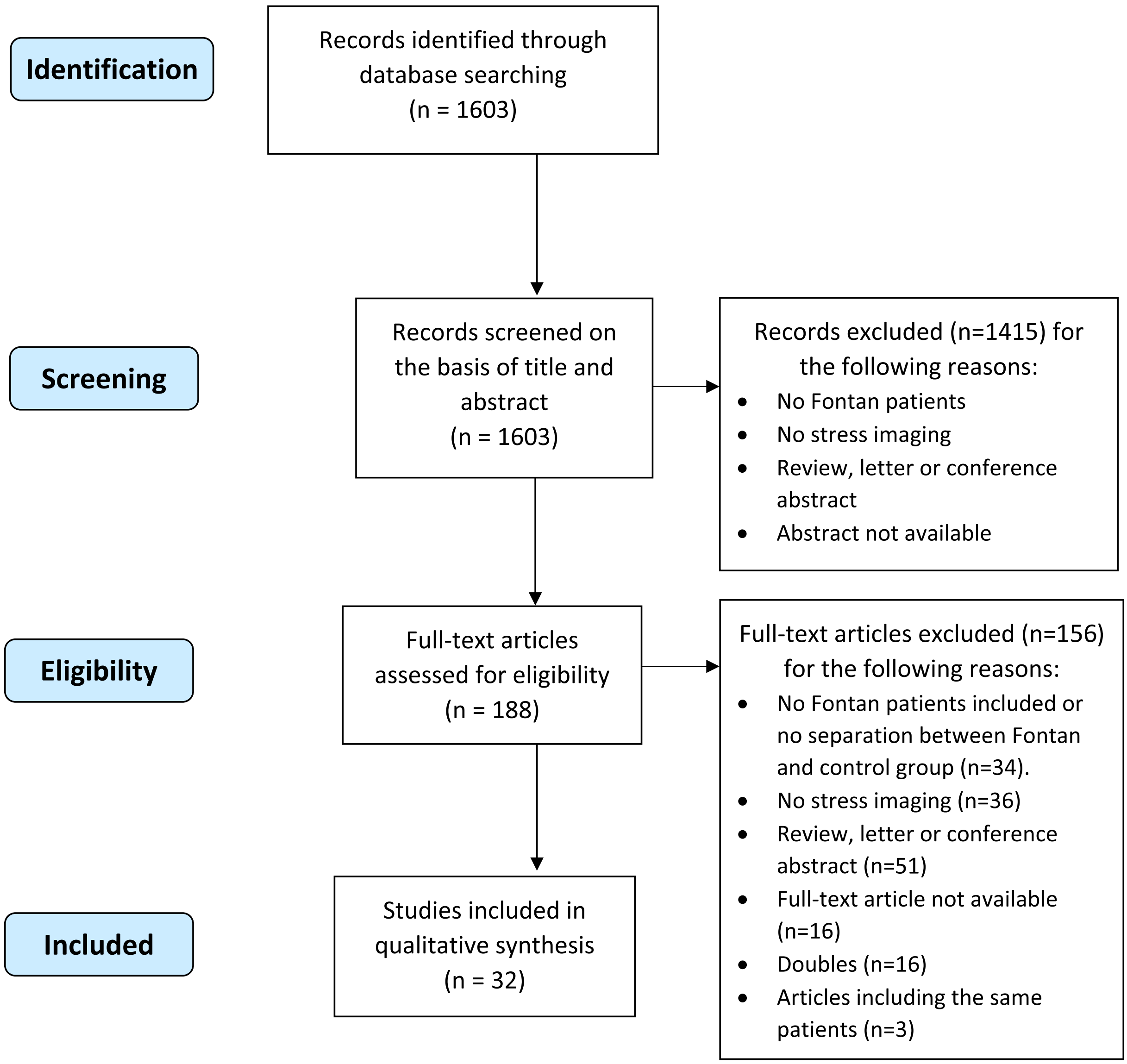

Fig. 1. Flowchart of the screening process.
Screening process of article screening, including reasons of exclusion.

showed a decrease in ESVi (mean decrease 24%) during stress.

A total of nine studies compared the cardiac stress response of Fontan patients with healthy controls [9,13,17,19,29–31,35,37]. All found decreased maximal heart rates and cardiac reserve in Fontan patients compared to controls. Four studies found decreased cardiac output during stress, including failure to further increase cardiac output after a certain intensity of exercise, whilst healthy controls were able to continue the increase of cardiac output during higher levels of exercise intensity [9,19,30,37]. Hjortdal et al. found that stress response between Fontan patients and healthy controls was comparable during submaximal exercise [13]. Brili et al. found that healthy controls reach their peak stroke volume at 10 mg/kg/min of dobutamine whereas Fontan patients at 20 microgram/kg/min [29]. Two studies measured a decreasing EDV during exercise in Fontan patients compared to controls [19,37]. Mkrtchyan et al. showed that ventricular–arterial coupling was impaired in Fontan patients at rest and during exercise compared with controls [17]. Both Yamazaki et al. and Hasan et al. used echocardiography and found decreased S′ velocity and inflow *E*-wave velocities and strain rates during rest and exercise in Fontan patients compared to healthy controls [31,35].

3.5. Difference between pharmacological induced and physical stress

No studies directly compared pharmacological induced stress and physical stress in Fontan patients. On average, stroke volume increased with 0.63% during pharmacological stress compared to an average increase of 11.86% during physical stress. The average increase in heart rate of patients in the dobutamine studies was +31 bpm (81.6 bpm vs 112.6 bpm) versus a mean of +42 bpm (75 bpm vs 117 bpm) with physical stress. EF increased with both types of stressors, more during dobutamine than with physical exercise (+15% vs 8%). With dobutamine stress EDV decreased (−14.2% rest vs exercise), with physical stress EDV increased slightly (+1.3%). ESV decreased more during dobutamine stress (−29% rest vs exercise) than with physical stress (−14.1%).

3.6. Cardiac response to different doses of stress

Only three studies reported on the effect of different doses of dobutamine [19,28,29]. Pushparajah et al. and Wong et al. found a greater decrease in stroke volume with higher doses of dobutamine [19,28]. Brili et al. found a greater increase in stroke volume until a

Table 1
Study Characteristics.

Author	Year	Study design	Patients (n)	Controls (n)	Type of controls / comparison	Imaging modality	Dose (μg/kg/min) or physical intensity	Type of stress	Positon	Type MRI/echo
Dobutamine magnetic resonance stress imaging										
Robbers-Visser et al. [20]	2008	Cross-sectional	32	0	n.a.	MRI	7.5	Dobutamine	Supine	1.5 T MRI-scanner (GE Medical Systems)
Romeih et al. [21]	2012	Comparative	7	7	PA with biventricular repair	MRI	5; 10; 15	Dobutamine	Supine	1.0 T MRI-scanner (Panorama; Philips Medical Systems)
Bossers et al. [38]	2014	Cross-sectional	69	0	n.a.	MRI	7.5	Dobutamine	Supine	1.5 T MRI-scanner (GE Medical Systems)
Pushparajah et al. [19]	2016	Cross-sectional	13	10	Healthy adults	MRI	10; 20	Dobutamine	Supine	1.5 T MRI-scanner with cardiac catheterization (Achieva; Philips).
Wong et al. [28]	2017	Cross-sectional	10	0	n.a.	MRI	10; 20	Dobutamine	Supine	1.5 T MRI-scanner (Achieva; Philips)
Kamphuis et al. [14]	2019	Cross-sectional	10	0	n.a.	MRI	7.5	Dobutamine	Supine	3 T MRI-scanner (Ingenia; Philips Healthcare)
Van den Bosch et al. [25]	2021	Cross -sectional	*97*	*36*	Patients without vs with event	MRI	7.5	Dobutamine	Supine	1.5 T MRI-scanner
van der Ven et al. [26]	2021	Cross-sectional	57	0	ECC vs ILT	MRI	7.5	Dobutamine	Supine	1.5 T MRI-scanner
Schmitt et al. [22]	2010	cross-sectional	10	0	n.a.	MRI + cath	10	Dobutamine	Supine	1.5 T MRI-scanner
Physical Exercise magnetic resonance stress imaging										
Pedersen et al. [18]/ Hjortdal et al. [45]	2002/ 2003	Cross -sectional	11	0	n.a.	MRI	0.5; 1.0 w/kg	Bicycle ergometer	Supine	1.5 T MRI-scanner (Philips NT)
Hjortdal et al. [13]	2008	Case -control	14	6	Healthy	MRI	0.5; 1.0 w/kg	Submaximal lower limb exercise	Supine	1.5 T MRI-scanner (Philips NT)
Van de Bruaene et al. [23]	2015	Cross -sectional	10	0	n.a.	MRI	Low: HR 100–110 Medium: HR 120–130 High: HR 140–150	Ergometer exercise	Supine	1.5 T MRI-scanner (Philips Achieva)
Khiabani et al. [15]	2015	Cross-sectional	30	0	n.a.	MRI	20 W increased with 20 W/ min to HR at VAT	Bicycle ergometer	Supine	1.5 T MRI-scanner (Avanto MRI; Siemens)
Mkrtchyan et al. [17]	2017	Case-control	13	13	Healthy	MRI	5 min submaximal cycling	Bicycle ergometer	Supine	1.5 T MRI-scanner (Avanto MRI; Siemens)
Wei et al. [27]	2017	Cross-sectional	11	0	n.a.	MRI	20 W increased with 20 W/ min to HR at VAT	Bicycle ergometer	Supine	1.5 T MRI-scanner (Avanto MRI; Siemens)
Avitabile et al. [7]	2018	Intervention study	13	0	n.a.	MRI	20 W increased with 20 W/ min to HR at VAT	Bicycle ergometer	Supine	n.a.
Biko et al. [8]	2019	Cross-sectional	48; 30 without AR; 18 with AR	0	n.a.	MRI	80% of HR obtained during maximal CPET	Exercise ergometer	Supine	1.5 T MRI-scanner (Avanto MRI; Siemens Medical)
Claessen et al. [9]	2019	Case-control	10	20	Healthy	MRI	Peakwattage in maximal CPET	Bicycle ergometer	Supine	CMR (type n.a.) + catheter
Contijoch et al. [10]	2020	Observational case series	4	0	n.a.	MRI	3 min at 20 W (4 rounds)	Stepping exercise	Supine	1.5 T MRI-scanner (Excite HD; GE Healthcare)

(*continued on next page*)

Table 1 (*continued*)

Author	Year	Study design	Patients (n)	Controls (n)	Type of controls / comparison	Imaging modality	Dose (μg/kg/min) or physical intensity	Type of stress	Positon	Type MRI/echo
Dobutamine echocardiography stress imaging										
Brili et al. [29]	2007	Case-control	10	10	Healthy subjects matched by sex; age & BSA	Echo	5; 10; 20; 30; 40	Dobutamine	n.a.	Echocardiographic system (Philips HP Sonos 2500)
Saiki et al. [33]	2019	Cross-sectional	35	0	n.a.	Echo	5	Dobutamine	n.a.	Echocardiographic system (SONOS 5500; Phillips)
Linden et al.[1] [32]	2021	Cross-sectional	19	0	n.a.	Echo	10	Dobutamine	n.a.	Echocardiographic system (Philips ie33)
Physical Exercise echocardiography stress imaging										
Cortes et al. [30]	1994	Clinical trial	16	18	Healthy peers	Echo	Submaximal: 18 min elapsed at 8.8 km/h and 20% incline	Progressive treadmill exercise	Standing / walking / sitting	Echocardiographic system (Yokogawa; RT-500)
Hasan et al. [31]	2017	Case-control	14	21	Healthy age matched	Echo	Adjusted for each patient	Bicycle ergometer	Sitting / upright	Echocardiographic system (Philips iE33)
Yamazaki et al. [35]	2021	cross-sectional	25	19	Healthy age- and gender-matched	Echo	20–25 W/ 3 min until 85% of maximal HR	Bicycle ergometer	Semi-supine	Echocardiographic system (GE Medical Systems; Vivid E9)
Intervention studies										
Cordina et al. [11]	2013	Intervention study	6	5	Fontan patients without training.	MRI	80% of (untrained) workoad	Bicycle ergometer	Supine	1.5 T MRI-scanner (Philips Medical Systems)
Van de Bruaene et al. [24]	2014	Intervention study	10	0	n.a.	MRI	Low: HR 100–110 Medium: HR 120–130 High: HR 140–150	Exercise	Supine	1.5 T MRI-scanner (Philips Achieva)
Duppen et al. [12]	2015	RCT	43	0	Fontan patients without training	MRI	7.5	Dobutamine	Supine	Locally available whole-body MRI
Laohachai et al. [16]	2017	Intervention study	14	0	n.a.	MRI	<50 kg; 10 W/min >50 kg; 15 W/min until exhaustion	Stepping exercise	Supine	1.5 T MRI-scanner (Phillips Intera)
Wittekind et al. [34]	2018	Intervention study	10	0	n.a.	Echo	Load based on patient, protocol until exhaustion	Bicycle ergometer	Upright	Echocardiographic system (GE Vivid 7)
Stress imaging using other imaging techniques										
Kondoh et al. [37]	1988	cross-sectional	10	13	Healthy controls or ex-Kawasaki disease patients	Single-crystal scintillation	10–15 W until exhaustion	Bicycle ergometer	Supine	Single-crystal scintillation camera (Siemens LEM-ZLC)
Harrison et al. [36]	1995	Case-control	47	8	Age-matched sedentary male subjects	Gated radionuclide angiography	548 kilopond-meters	Bicycle ergometer	n.a.	Apex 409 Elscint camera

CMR = Cardiac Magnetic Resonance Imaging; kg = kilogram; min = minute; MRI = Magnetic Resonance Imaging; n.a. = not applicable; PVR3DE = pressure-volume relations 3D-echocardiography; PVRCond = pressure-volume relations conductance technology; ToF = Tetralogy of Fallot; VAT = ventilatory anaerobic threshold W=Watt, AR = aortic reconstruction.

[1] Outcomes are of patients with Fontan and Glenn circulation combined.

dobutamine dose of 20 μg/kg/min (healthy controls had their peak stroke volume already at 10 μg/kg/min), followed by a lower increase compared to rest at dobutamine levels of 30 μg/kg/min and a decreasing stroke volume at 40 μg/kg/min [29]. Three physical exercise studies reported on the effect of different levels of intensity [13,18,23]. Hjortdal et al. showed that aortic flow and inferior caval vein flow increased with higher levels of exercise, whereas superior caval flow remained unchanged [13]. Pedersen et al. found an increase in stroke volume with higher levels of exercise intensity while Van de Bruaene et al. only found an increase of stroke volume during low intensity exercise, and a decrease of stroke volume compared to rest values in moderate and high exercise [18,23]. The studies with the largest increase in stoke volume (47.2% and 15%) were both echocardiographic studies [10,29].

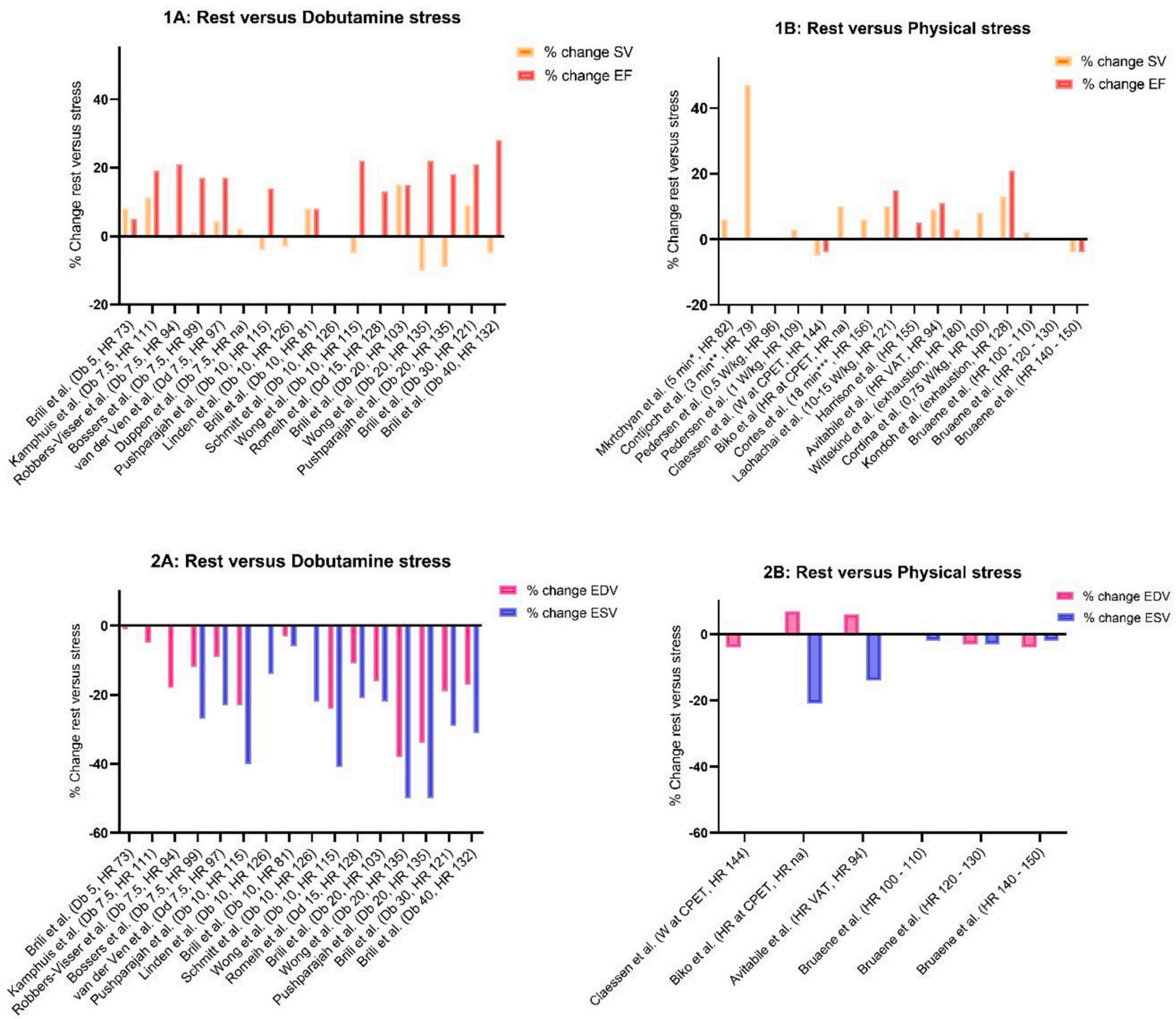

Fig. 2. Change in SV, EF, EDV and ESV after stress.
1A: change in SV and EF rest versus dobutamine stress, 1B: change in EDV and ESV rest versus dobutamine stress, 2A: change in SV and EF rest versus physical stress, 2B: change in rest in EDV and ESV rest versus physical stress.

3.7. Adverse events

Most studies did not report on adverse events. Four studies reported no adverse events. A total of four studies reported change in protocols due to side-effects of stress imaging in 15 patients [14,20,32,38]. All of these studies used pharmacological induced stress. Reported reasons to lower or stop dobutamine administration (in 3 studies) were: an increase in heart rate > 50% compared to rest ($n = 6$) or blood pressure increase of >50% compared to rest ($n = 1$), severe headache (n = 1) and frequent ventricular extrasystoles ($n = 3$) [14,20,38]. All of the side effects disappeared after stopping dobutamine administration. In the fourth study, a conductance catheter caused an arrhythmia in 4 patients [32].

3.8. Differences between different types of Fontan procedures

Six studies compared the cardiac response to stress in different surgical approaches to the Fontan circulation [8,13,20,26,33,38]. Biko et al. compared Fontan patients with a reconstructed aorta to those without a reconstructed aorta [8]. Pulse-wave velocities (speed of the systolic bolus of blood into the vasculature), ventricular afterload and aortic stiffness were increased in Fontan patients with an aortic reconstruction both at rest and during exercise. Saiki et al. found that patients with presence of an naturally closed fenestration had better ventricular-arterial coupling compared to patients with an open fenestration during stress [33]. Three studies compared stress response in patients with an extra-cardiac conduit connection (ECC) versus intra-atrial lateral tunnel (ILT) [13,26,38]. Hjortdal et al. found higher increases in heart rate during submaximal stress in patients with an ILT compared to an ECC, other cardiac parameters were comparable [13]. Bossers et al. found that ECC patients have a higher ejection fraction and cardiac index, together with a lower afterload during dobutamine stress compared to ILT patients [38]. Van der Ven et al. showed that maximal atrial volumes decreased for ECC patients during dobutamine stress, whereas ILT patients increased maximal volume [26]. Similarly, atrial conduit volume increased for ECC patients and decreased for ILT during dobutamine stress. Bossers et al., Robbers-Visser et al. and Ven et al. compared patients with a dominant left ventricle (LV) and right ventricle (RV) during stress [20,26,38]. Van der Ven et al. did not find differences in atrial function between dominant RV or LV patients during stress [26]. Both Bossers et al. and Robert-Visser et al. showed that patients with a dominant LV had a higher EF during stress, other cardiac outcomes (ESV, EDV, SV) were comparable [20,38].

3.9. Predictive value of stress imaging

Six studies investigated relations between the cardiac response to stress and (adverse) outcomes in Fontan patients [7,14,21,25,26,39]. Van der Ven et al. found that the reserve (change from rest to stress) of early emptying of the atria during stress is related to exercise capacity in patients with an ECC [26]. Van den Bosch et al. found that Fontan patients with lower increase in ejection fraction during stress had a higher risk of developing cardiac events during follow-up, whereas previously identified predictors (end-diastolic volume index >125 mL/m2, peak Vo2, NT-proBNP) did not relate to a higher risk in their study population [39]. In Fontan patients with pulmonary atresia and intact ventricular septum, a strong correlation between stroke volume during stress and oxygen pulse and consumption during exercise testing was found by Romeih et al. [21]. Kamphuis et al. found a negative correlation between higher intraventricular viscous energy loss, kinetic energy and vorticity during stress imaging (using 4D flow CMR) and maximal exercise capacity [14]. Avitabile et al. found a strong correlation between leg lean mass *Z*-score and improved systemic output in stress [7].

3.10. Effects of interventions on cardiac stress response

Five studies used stress imaging to investigate the effects of an intervention aimed at improving cardiac stress response [11,12,16,24,34]. Van de Bruaene et al. showed that treatment with sildenafil improved cardiac index during submaximal exercise with a decrease in total pulmonary resistance and an increase in stroke volume [24]. Four studies researched effects of exercise interventions on stress response in Fontan patients. Wittekind et al. showed that average heart rate in Fontan patients during submaximal exercise became lower (180 vs 171 bpm) after a cardiac rehabilitation program consisting of aerobic training and low-weight resistance training, whereas stroke volume remained unchanged [34]. Duppen et al. investigated the effects of a 12-week aerobic exercise training program, which consisted of three 1-hour exercise sessions per week, and did not show any significant changes of the cardiac stress response in Fontan patients after training [12]. Laohachai et al. performed exercise CMR after 6 weeks of inspiratory muscle training and showed improvements at resting cardiac output in patients with a Fontan circulation. However in that study cardiac output did not improve during stress [16]. Lastly, Cordina et al. showed improved cardiac filling and stroke volume (75 vs 91 mL) during stress in patients with a Fontan circulation after a 6 months detraining period following a 12 week resistance training program ($n = 4$) [11].

4. Discussion

This systematic review provides an overview of 34 studies investigating stress imaging methods and cardiac response in 728 Fontan patients. Stress imaging methods in Fontans could be categorized in four major groups: CMR or echocardiography in combination with the use of dobutamine administration or physical exercise using a bicycle ergometer. No major adverse events were reported, although many studies did not report on adverse events. Cardiac response to stress in Fontan patients differed from healthy subjects, including lower increase in heart rate, decrease in EDV and decreased cardiac output, especially during higher levels of exercise.

4.1. Cardiac stress response in Fontan patients

In a healthy biventricular heart, increase in cardiac output during stress is initially achieved by an increase in stroke volume, mediated by synergetic increase in cardiac contractility and cardiac filling (preload), while a continuous rise in HR mediates further increases in cardiac output [40]. In the studies included in our review, cardiac function during rest in Fontan patients was relatively well preserved with a generally normal or modestly reduced cardiac output (mean indexed stroke volume at rest was 44 mL, while normal values for girls and boys are 44 [40–48] and 51 ml [45–48]) respectively) [41]. Most included studies (71%) reported an normal increase in stroke volume during submaximal exercise. However several studies reported that Fontan patients failed to further augment cardiac output with increasing exercise intensity. A total of 6 studies even reported a decrease in stroke volume during (higher levels) stress. In almost all studies (irrespective of the type of stressor), Fontan patients increased their HR and EF during stress, and decreased ESVi, compatible with enhanced systolic function. EDVi decreased in all studies during stress, in contrast to enhanced preload during exercise in healthy subjects. These findings confirm that exercise intolerance in Fontan patients is mostly explained by impaired preload, rather than abnormal systolic contractile function. Impaired preload and diastolic dysfunction in Fontan patients may be explained by multiple factors, including lack of a sub-pulmonary pump, impaired transpulmonary flow, impaired atrial function, delayed ventricular relaxation and abnormal compliance and higher end diastolic pressure [42–44]. Due to the lack of the sub pulmonary pump, cardiac filling in Fontan patients at rest relies heavily on inspiration. Three of the studies included in the current review looked at the effect of inspiration on cardiac filling during stress, showing a higher inspiratory flow fraction over the inferior caval vein in Fontan patients compared to controls at rest and during exercise. However during exercise the peripheral muscle pump seemed to have a more prominent role in increasing venous return [23,27,45]. In several studies, different types of Fontan circulations were compared. In summary, patients with a dominant LV and ECC had a higher EF compared to RV and ILT patients. A better EF in dominant LV Fontan suggests a dominant LV is better equipped to support the systemic circulation at the long term, leading to improved exercise capacity and survival compared to dominant RV [46].

4.2. Difference between dobutamine and physical stress

In this systematic review, 21 of included studies used physical stress. A total of 316 Fontan underwent physical stress imaging compared to 412 patients who underwent pharmacological stress imaging. Physical stress imaging replicates hemodynamic changes at physical exercise better compared to pharmacological stress. However, physical exercise is more time consuming, complicated to use in younger children and hard to perform during imaging, especially if executed in the spatially limited MRI environment [47]. As movement during imaging interferes with image quality, scans were mostly obtained right after exercise instead of during actual exercise. When comparing physical to pharmacological stress response of Fontan patients, several differences appear. Heart rate and stroke volume increased less with pharmacological stress imaging compared to physical stress (HR +39% versus +57% and SV +0.6% versus +11.9%), suggesting that with physical exercise higher levels of exercise intensity and thus cardiac effort were obtained. EF increased the most and ESV decreased the most during dobutamine induced stress compared to physical stress (EF +15% versus +8% and ESV -28% versus −14%). The larger increase in EF and decrease in ESV during dobutamine induced stress can be explained by the fact that dobutamine (a catecholamine) enhances cardiac contractility. The greater decrease in EDV during dobutamine admission might be explained by the fact that the diastolic inflow into the ventricle is not augmented by the peripheral muscle pump during dobutamine induced stress. This muscle pump is an important enhancer for venous return in

Fontan patients during exercise. Furthermore, neurohormonal responses may differ between physical and dobutamine stress [45]. An unsolved issue in both physical stress CMR and pharmacological stress CMR is standardization of protocols. The physical stress studies included in this systematic review used different devices (including cycling or push-pull ergometers) and exercise-intensities (based on workload or heart rate zones), positions and even timing of scanning (during exercise or right after exercise) was different. Although stress imaging using dobutamine should be easier to standardize, almost all included studies in this systematic review used different dobutamine doses ranging from 5 to 40 μg/kg/min [48].

4.3. Safety

Surprisingly, most studies did not report on adverse events. The number of reported adverse was low. Of the 728 (unique) Fontan patients reviewed, in only 13 patients the imaging procedure had to be stopped or required changes to the protocol due to a side effect /adverse event. One of these events was an arrhythmia caused by a conductance catheter, the other 12 were dobutamine induced. The abnormalities were discomfort, high blood pressure, substantial increase in heart rate, headache and frequent ventricular extra systoles. All side effects disappeared after lowering or stopping dobutamine infusion. Therefore we conclude, that both methods can be used safely, but patients must be strictly monitored when dobutamine admission is used.

4.4. Limitations

The included studies differ in outcome measurements used, measurement techniques, observers and most importantly levels of intensity. The included population also was heterogeneous, with differences in age, diagnosis before Fontan, physical activity levels and cardiac function. This makes it hard to interpret the absolute values (SV, EDV, ESV and EF) between studies and made it impossible to perform a meta-analysis. To partly overcome this problem, we calculated and compared weighted change in cardiac parameters instead of change in absolute values. The majority of the studies did not include a healthy control group. We could not rule out overlap of patients between studies for all studies included in our review. Wong et al. and Pushparajah et al. both from the same institution possibly included overlapping patients. The same applies to the studies of Avitabile et al., Wie et al. and Khiabani et al.. Van der Ven et al., Bossers et al. and Robbers-Vissers et al. partly included the same patients from Erasmus MC – Sophia children's hospital in the Netherlands, but investigated different outcomes at different time-points during these patients' follow-up [20,26,38]. Van de Bruaene et al. (2015), Van de Bruaene et al. (2014) and Cleassen et al. most likely included some of the same patients, but looked at different outcomes, patients were only included in the calculations once [9,23,49]. Lastly, both Bosch et al. (2019 and 2021) and Hjortdal et al./ Pederson et al. (2002 and 2003 and 2008) published 3 articles most likely including the same stress imaging tests, respectively [25,50] and [13,18,45].

4.5. Clinical application and future studies

As failure of the Fontan circulation is common, early identification of Fontan patients at risk for poor cardiac function is key in this population [51]. Studies investigating the added value of stress imaging in Fontan patients (and other congenital heart diseases) are scares. Currently, we could only identify five studies researching the relations between stress imaging and (adverse) outcomes. Two studies found that a better increase in stroke volume during stress led to a better exercise capacity, an important prognostic predictor of morbidity and mortality [52]. Only one study investigated the prognostic value of (abnormal) cardiac response to stress in relation to (long-term) Fontan complications, and found a higher risk of developing cardiac events during follow-up in Fontan patients with lower ejection fraction increases during stress. Future studies should be prospective and longitudinal / serial, in order to provide a better understanding of cardiac stress response over time. This might lead to better insights of the added clinical value of cardiac stress testing, in addition the better understand of the stress physiology (development) of Fontan patients.

5. Conclusion

Exercise stress imaging shows an abnormal response to exercise in Fontan patients compared to healthy controls, which was more pronounced during higher exercise intensities. Overall SV, EF and HR increased during exercise, whereas a decrease in ESV and abnormal decrease in EDV were seen. When comparing pharmacologically induced stress to physical stress, the latter one seems better suited to obtain high intensities. Stress imaging was safe with only minor adverse events, all reported during dobutamine stress imaging. Knowledge on the change of cardiac stress response over time and the clinical application of stress imaging in Fontan patients remains limited. Future studies should further clarify the added prognostic and clinical value of stress imaging in this unique patient group.

Funding statement

This study was not funded.

Author contributions

LES and WAH designed the study. CL and WvP did the literature search, performed title and abstract screening and data extraction. LES had the main role in drafting the manuscript. LEB and WAH contributed to interpretation. All authors (CL, WvP, LES, LEB and WAH) critically revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship and that no others meeting the criteria have been omitted.

Conflicts of interest disclosure

Authors have no conflicts of interest to declare that are relevant to the content of this article.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgements

The authors wish to thank Wichor Bramer (Erasmus University Medical Center) for his assistance with the literature search, and Anaelle Snijders for her contribution.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131192.

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