Review Article

Impact of cardiovascular magnetic resonance in single ventricle physiology: a narrative review

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Background and Objective: Cardiovascular magnetic resonance (CMR) is a routine cross-sectional imaging modality in adults with congenital heart disease. Developing CMR techniques and the knowledge that CMR is well suited to assess long-term complications and to provide prognostic information for single ventricle (SV) patients makes CMR the ideal assessment tool for this patient cohort. Nevertheless, many of the techniques have not yet been incorporated into day-to-day practice. The aim of this review is to provide a comprehensive overview of CMR applications in SV patients together with recent scientific findings.

Methods: Articles from 2009 to August 2024 retrieved from PubMed on CMR in SV patients were included. Case reports and non-English literature were excluded.

Key Content and Findings: CMR is essential for serial follow-up of SV patients and CMR-derived standard markers can improve patient management and prognosis assessment. Advanced CMR techniques likely will enhance our understanding of Fontan hemodynamics and are promising tools for a comprehensive patient evaluation and care.

Conclusions: There is increasing research that shows the advantages of CMR in Fontan patients. However, further research about the prognostic role of CMR in older Fontan patients and how new methods such as modeling and deep learning pipelines can be clinically implemented is warranted.

Keywords: Congenital heart disease; single ventricle (SV); Fontan circulation; cardiovascular magnetic resonance (CMR)

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Introduction

Background

Cardiovascular magnetic resonance (CMR) is an essential part of the surveillance algorithm in adults with a Fontan circulation (1,2). The CMR portfolio is increasing steadily and allows to accurately assess function, volumes and tissue characteristics of the single ventricle (SV), to evaluate the anatomy of the underlying congenital heart defect (CHD) as well as to investigate Fontan connections and hemodynamic

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variables.

Rationale and knowledge gap

Patients can be easily monitored over time with the use of CMR and an increasing number of studies demonstrate that CMR is able to improve long-term assessment and prognostication in Fontan patients (3-7). Modern machine learning and modelling techniques are expanding the field and it is expected that CMR acquisition and analysis will not only become faster (8-10), but that these techniques will also allow to ameliorate management and risk stratification in Fontan patients as first studies already suggest (11,12). However, not only the heart and the Fontan connections can be assessed, CMR is also more and more used to improve treatment and understanding of Fontan associated complications such as plastic bronchitis (PB) and protein losing enteropathy (PLE) with lymphatic angiography seems to become an integral part of the CMR protocol (13,14). Catheter CMR is another promising approach but so far, it is only used in few centres worldwide (15-17). Although the usefulness of CMR in SV patients is undoubted, there are a variety of techniques that have not yet been fully incorporated into routine clinical practice and their impact has not yet been fully explored.

Objective

In this review, an overview of the newest state of knowledge about how to use CMR and what we can expect from it now and in future in the growing group of patients with a Fontan circulation. We present this article in accordance with the Narrative Review reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-409/rc).

Methods

For this narrative review, a literature search on PubMed covering the period from 2009 to August 2024 was performed. The search strategy including the search terms is shown in *Table 1*.

CMR in SV patients—standard and novel techniques

Assessment of anatomy

Standard and advanced protocols for SV evaluation together with explanation of all sequences and addressing numerous challenges has been recently published and serves as a guide for every physician who performs CMR scans in patients with Fontan circulation (2). Cross-sectional imaging with CMR is an ideal modality for assessing complex anatomy of Fontan patients. Dark-blood and bright-blood single shot imaging, cine imaging, 3D whole heart steady state free precession or contrast enhanced angiography are used to assess anatomy and patency of the Fontan pathways and intracardiac morphology and connections (*Figures 1*,*2*). Thrombus, an important complication, can be seen using early gadolinium enhancement sequence (2,18). Ventricular morphology can be identified by assessing the typical morphological features of the left and right ventricles (19). This is of importance as a morphologically right ventricle is associated with a worse outcome as shown by cohort and CMR studies (20,21).

Assessment of SV hemodynamics and ventricular function

CMR is the gold standard for volumetric analysis of Fontan ventricles with broad morphological range. As standard, Simpson disk summation method is used for calculation of the volumes from the short axis cine stack (*Figure 3*) (2). CMR reference values for volumes and right ventricular mass are available for patients with hypoplastic left heart syndrome until the age of 25 years (22). Indexed right ventricular volumes significantly increase over time already during childhood whereas ejection fraction does not decrease as much (7). A rapid increase in indexed end-diastolic volumes has been associated with adverse outcomes (21). Therefore, serial volumetric assessment is important and might be of greater value than measurement of ejection fraction (7). Volumes and mass of the SV can be applied for calculation of ventricular global function index which was found to be a very useful prognostic clinical marker associated with Fontan failure and exercise capacity (23).

Besides the standard measurements, advanced parameters have been explored which can serve as preclinical markers of deterioration or markers of Fontan failure. Postprocessing analysis of myocardial deformation is performed using feature tracking software. Myocardial deformation indices are impaired in single left ventricles when compared to healthy controls (24). There is also a difference between left and right SVs with single left ventricles demonstrating higher global circumferential strain and lower global longitudinal strain than right ventricles (25). Importantly, myocardial strain of SVs correlates with clinical markers

Table 1 The search strategy summary

Items	Specification
Date of search	01/05/2024 to 01/08/2024
Databases and other sources searched	PubMed
Search terms used	Single ventricle and Fontan circulation in combination with • Cardiovascular magnetic resonance • Magnetic resonance imaging • Lymphangiography • Fibrosis • Myocardial fibrosis • Prognosis • Computational fluid dynamics • Modeling • Ventricular function • Anatomy • 4D Flow
Timeframe	2009–2024
Inclusion and exclusion criteria	Inclusion criteria: original articles, reviews, and expert consensus; articles in English Exclusion criteria: case reports and articles not in English or not translated into English
Selection process	The selection process was conducted independently by the authors, who reached a consensus in a final meeting

and NT-pro-BNP (25). Atrial strain assessed with CMR is also associated with adverse clinical outcome and cardiac catheterisation measures such as cardiac index and end-diastolic pressure (26).

Aortopulmonary collaterals have been found to be present in all patients with SV physiology before and after Fontan completion, however their amount spontaneously decreases once the Fontan circuit is established. Clinical relevance of the degree of collateralisation in Fontan patients is not entirely clear, however, CMR allows accurate measurement of the flows using numerous 2D flow acquisitions. Currently recommended and validated preferred single 4D Flow sequence enables faster acquisition with very good agreement between 2D and 4D Flow measurements (27,28). Interestingly, it has been found that indexed aortic and cavopulmonary flows are decreasing whereas ejection fraction does not decline significantly over period of 10 years (29).

CMR volumetric and functional parameters correlate with exercise capacity in Fontan patients. Cardiac index is inversely associated with a decrease in peak VO_2 over time. Cut-off values of indexed end-diastolic volume of >101 mL/m^2 and indexed end-systolic volume >47 mL/m^2 are associated with impaired cardiopulmonary capacity (4). Stress CMR connects assessment of the functional status with comprehensive CMR data and can be performed with physical exercise or with continuous dobutamine infusion. Hypoplastic left heart patients post Fontan completion fail to increase cardiac index at high doses of continuous dobutamine even when inhaled nitric oxide is added. This is caused by limited preload with falling end-diastolic volumes during exercise confirming the known fact that the pulmonary perfusion is the limited factor of the Fontan circuit rather than SV myocardium (30,31). Another study using stress CMR with ergometer has shown that ventriculoarterial coupling is impaired in Fontan patients at rest and although it improves during exercise, it remains impaired when compared to healthy controls (32). Moreover, patients with a morphological right ventricle have worse response during exercise than those with single

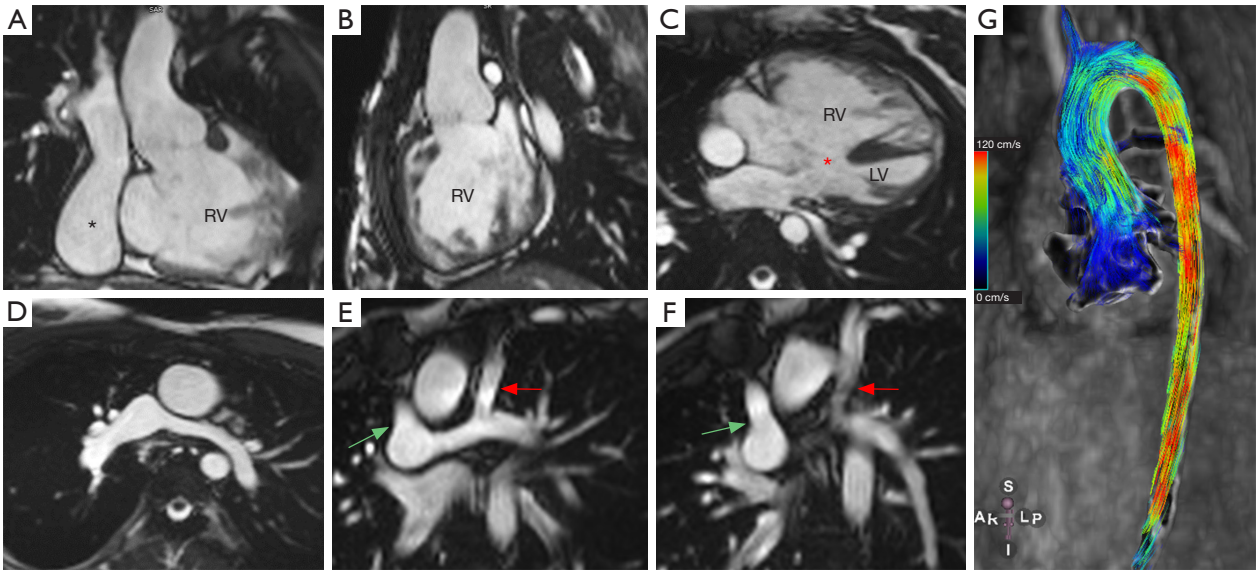

Figure 1 Female with double outlet right ventricle, hypoplastic left ventricle, large ventricular septal defect (C, red asterisk) and left persistent superior vena cava. (E,F) She has a right-sided upper cavopulmonary connection (green arrows) and a left-sided Glenn anastomosis (red arrows). Fontan completion was established with creation of an intraatrial lateral tunnel (A, black asterisk). CMR cine imaging is able to delineate the detailed anatomy (A-F) and to assess blood flow dynamics (G). RV, right ventricle; LV, left ventricle; CMR, cardiovascular magnetic resonance.

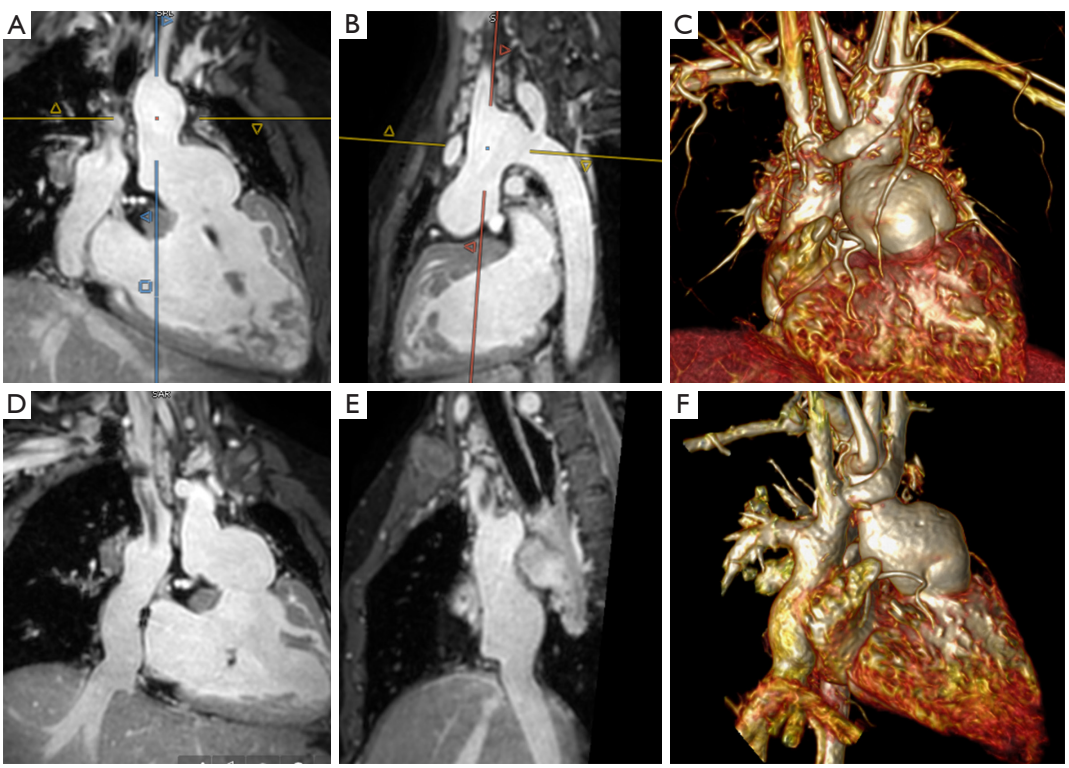

Figure 2 Non-contrast angiographic images acquired with 3D modified Dixon sequence in a patient with hypoplastic left heart syndrome. Multiplanar and 3D reconstruction shows the neo-aorta and descending thoracic aorta (A-C) as well as the total cavopulmonary connection (D-F).

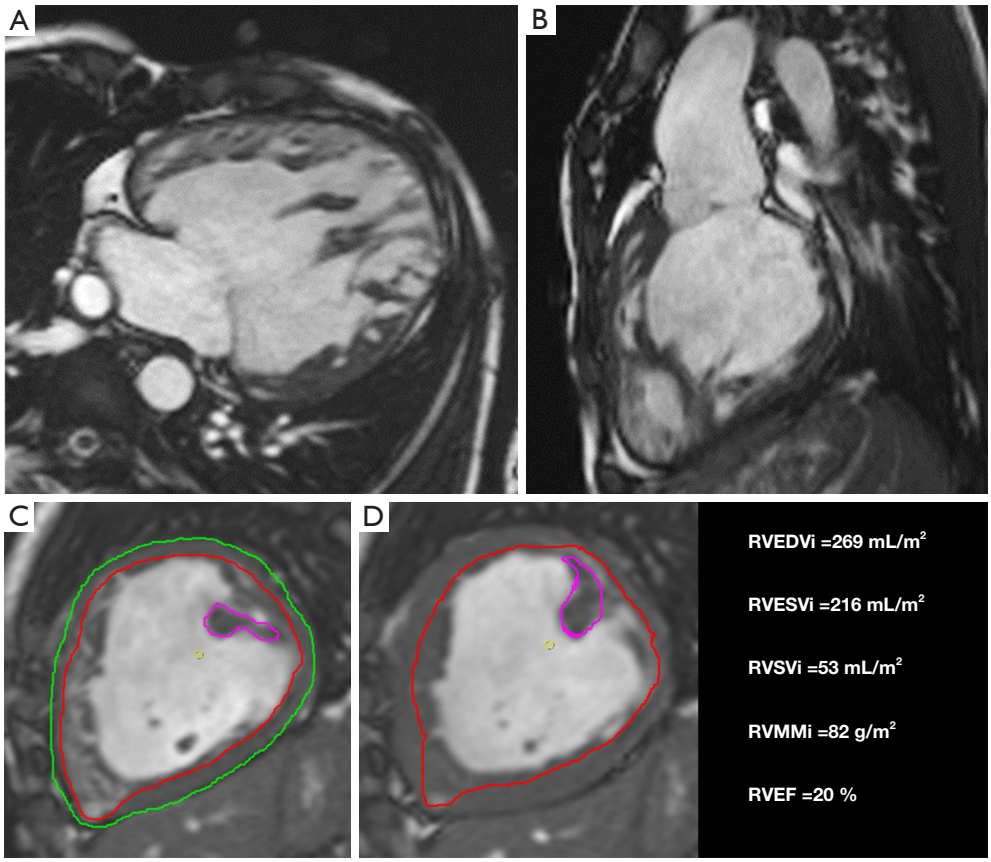

Figure 3 Young male adult with systemic right ventricular dysfunction. CMR Cine imaging shows a severely dilated and hypertrophied right ventricle (A,B). Ventricular volumetry from short axis images demonstrated an RV ejection fraction of only 20% (C,D). CMR, cardiovascular magnetic resonance; RV, right ventricle; RVEDVi, right ventricular end-diastolic volume index; RVESVi, right ventricular end-systolic volume index; RVSVi, right ventricular stroke volume index; RVMMi, right ventricular mass index; RVEF, right ventricular ejection fraction.

left ventricle (33).

4D Flow has been extensively used for routine clinical examinations and for research purposes. Kinetic energy, energy loss and energy loss index (calculated as energy loss divided by kinetic energy) correlate with reduced exercise capacity and are superior to ejection fraction and cardiac index (34,35). Vortical flow is associated with significantly increased viscous energy loss in Fontan patients and the confluence and left pulmonary artery are mainly affected (36). Patients with hypoplastic left heart syndrome after Fontan completion were found to have neo-aortic arch with abnormal twist and helical flow patterns when compared to healthy controls and the maximum twist correlates with increased right ventricle myocardial mass (*Figure 4*) (37).

Myocardial fibrosis

Myocardial tissue characterisation is a key strength of CMR and enables the detection and quantification of replacement and interstitial myocardial fibrosis (38-41). Late gadolinium enhancement (LGE) imaging (replacement fibrosis) and T1 mapping allow the calculation of extracellular volume fraction (interstitial fibrosis) and are the most common CMR techniques that are used for fibrosis assessment (38-41). New developments include magnetic resonance fingerprinting (42) and synthetic LGE images that are created from T1 mapping images (43,44) have shown clinical potential in non-congenital cardiac disease but have not yet been applied to Fontan patients.

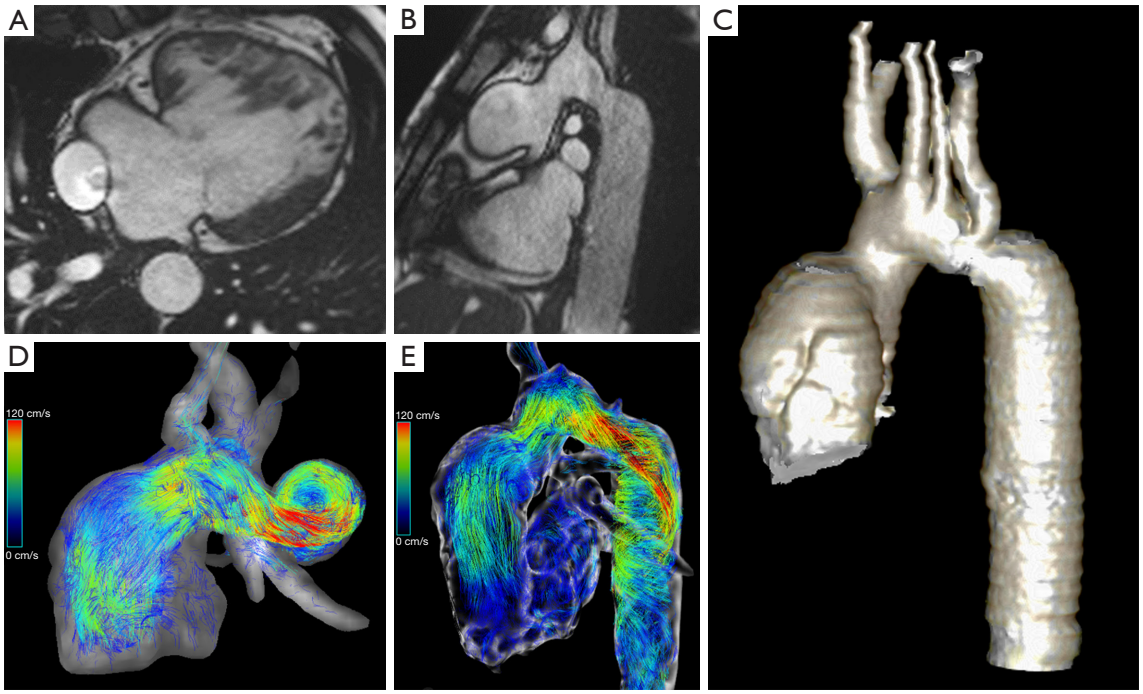

Figure 4 Male with hypoplastic left heart syndrome and a caliber jump in the aortic arch (A,B). The descending thoracic aorta is dilated (B,C) likely related to an increased helical flow in the descending thoracic aorta that develops in the aortic arch (D,E).

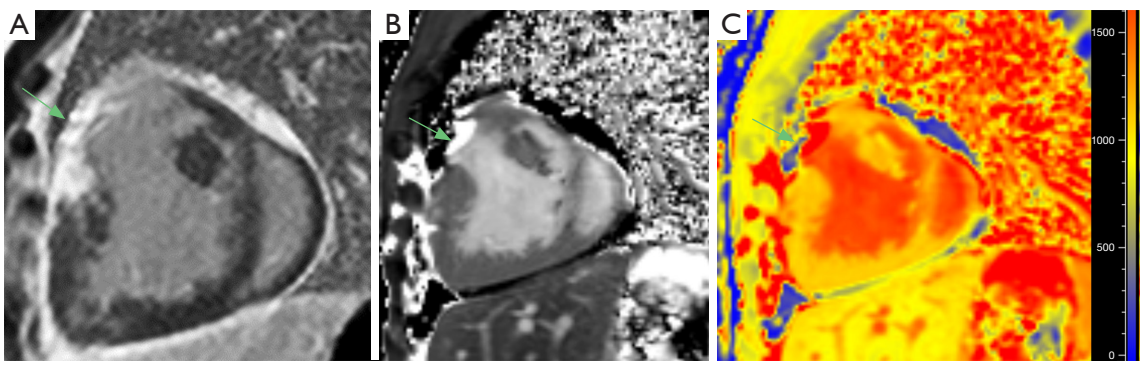

Figure 5 Male with hypoplastic left heart syndrome in Fontan circulation who underwent Norwood operation with Sano modification. There is replacement fibrosis in the right ventricular free wall detected on late enhancement images in the area of the previous Sano shunt (A, green arrow). High T1 values (~2,500 ms at 3 Tesla) are detected by native T1 mapping in the same area (B,C, green arrows).

In the clinical context myocardial fibrosis is associated with ventricular dysfunction, arrhythmias and sudden cardiac death in patient with various CHD (45-47). Studies have also shown that the detection of myocardial fibrosis can help in risk prediction in SV patients (*Figure 5*). Rathod *et al.* (48) found that LGE was common in Fontan patients and that those that were LGE positive, had a lower mean ejection fraction, increased SV end-diastolic volume and mass as well as higher frequencies of regional wall motion abnormalities and non-sustained ventricular tachycardia. More recent studies used T1 mapping (*Figure 5*) and could show that SV patients have increased myocardial T1 values and extracellular volume fraction that are associated with decreased myocardial contractility and worse clinical outcome (49-51). Potential reasons for the occurrence of fibrosis in SV patients have not been well explored, a recent study on patients with hypoplastic left heart syndrome suggests an impaired coronary microcirculation of the

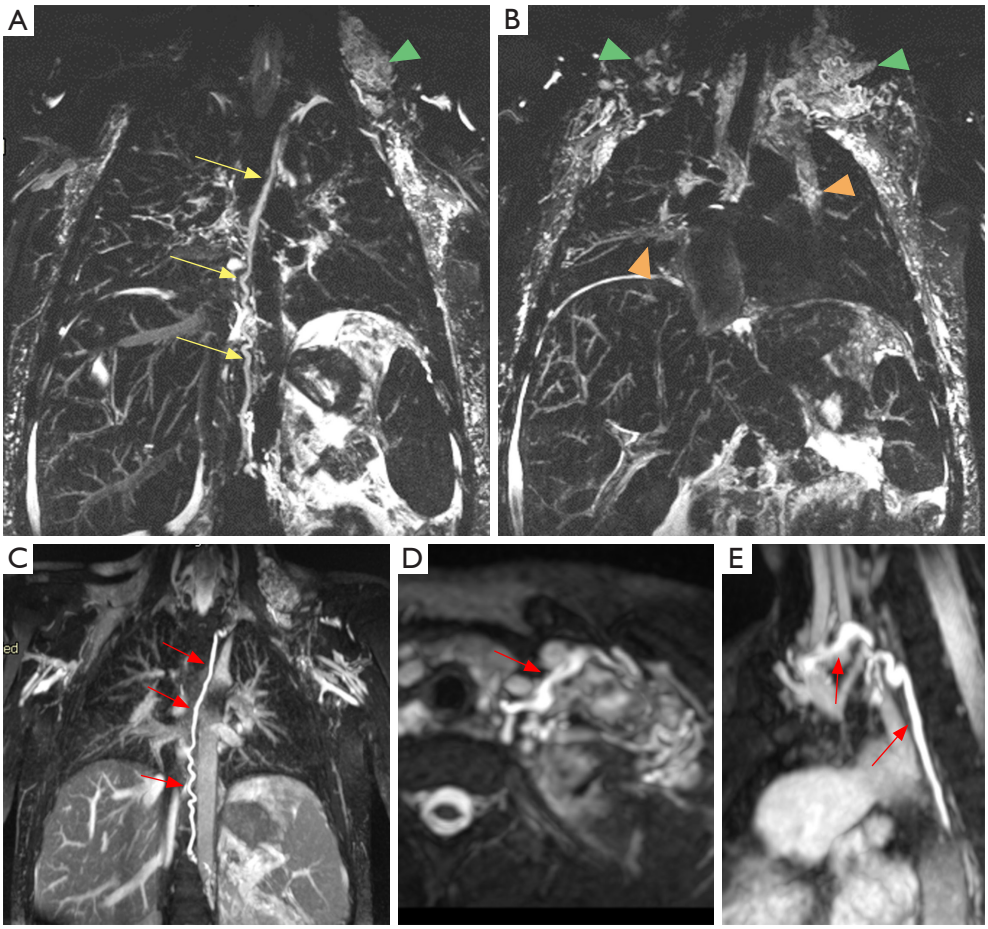

Figure 6 Adult female with protein losing enteropathy in Fontan circulation. High T2-weighted imaging (A,B) shows a dilated thoracic duct measuring 4 mm (A, yellow arrows) and abnormal lymphatic tissue bilaterally in the supraclavicular region (green arrowheads) extending into the lungs (orange arrowheads). Improved visualization of the thoracic duct (red arrows) can be reached with 3D steady state free precession sequence (C-E). The thoracic duct can be followed throughout its entire course in the upper chest with no obvious stenosis seen (D,E). The patient was treated with sildenafil and heart failure medication including diuretics.

systemic right ventricle and could demonstrate that the frequency of LGE increased over time (52). However, further studies are required to better understand the clinical utility of CMR fibrosis imaging and in SV patients.

Magnetic resonance lymphangiography (MRL)

Increased lymph production and impaired lymphatic drainage are both related to the elevated systemic venous pressures in Fontan patients and can cause serious lymphatic complications such as PLE, PB, ascites and pleural effusion (53,54). PLE and PB are severe diseases that are associated with poor prognosis (55,56). MRL with non-contrast T2-weighted techniques is a developing method that has been more recently recommended for the routine assessment of Fontan patients (1) (*Figure 6*). This method cannot only help to better understand the lymphatic anatomy and types of lymphatic changes in Fontan patients, but it is essential in the developing area of lymphatic interventions (13,57). Dynamic contrast-enhanced MRL provides dynamic information about the central lymphatic system and is performed with T1-weighted imaging after application of gadolinium-based contrast agent via a groin lymph node (58). This dynamic technique is especially helpful for treatment planning of lymphatic complications (59,60) and further developments of the method suggest that intrahepatic or intramesenteric contrast application may have advantages in patients with PLE (61,62).

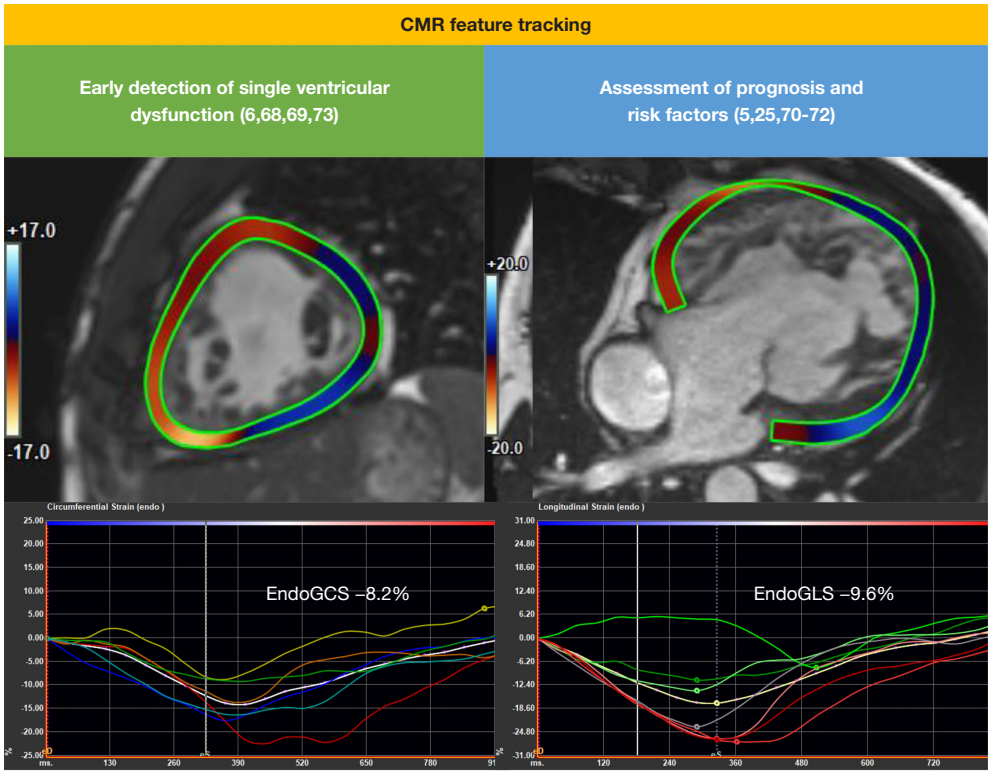

Figure 7 CMR feature tracking has been shown to help in early detection of ventricular dysfunction (6,69-71) and in the assessment of prognosis and risk factors (5,25,72-74) in patients with a single ventricle. Example curves for global endocardial circumferential and longitudinal strain are demonstrated. CMR, cardiovascular magnetic resonance; EndoGCS, endocardial global circumferential strain; EndoGLS, endocardial global longitudinal strain.

Static T2-weighted imaging is useful to evaluate the anatomy of the thoracic duct and the lymphatic changes in SV patients before and after Fontan completion (13,61). Static T2-weighted MRL can be accompanied by a 3D balanced steady stated free precession sequence to improve the visibility of the thoracic duct (63) (*Figure 6*).

Prognostic role of CMR in SV patients

An increasing number of SV patients with a Fontan circulation grew up and reach adulthood. However, morbidity and mortality are high with single right ventricular patients having a worse clinical outcome (20,64,65). CMR allows a comprehensive investigation of Fontan connections, ventricular function and hemodynamics and a paucity of studies have shown that it can help in risk stratification and prognosis assessment.

CMR-derived systemic ventricular volumes are related to worth outcome and an indexed end-diastolic SV volume >125 mL/m^2 has been shown to be an independent predictor for death or transplant late after the Fontan completion (3). In a study analysing serial CMR studies, the same group could show that Fontan patients with rapid increase in (>5 mL/body surface area$^{1.3}$/year) may have a higher risk of adverse outcomes (21). In patients with a biventricular Fontan circulation stroke volume ratio was associated with worse outcome parameters (66).

Flow assessment either using 2D or 4D phase contrast mapping can help to understand the Fontan hemodynamics and several flow parameters have been related to Fontan outcomes. Especially the degree of collateral has been shown to be disadvantageous and can lead to SV volume overload (67,68).

CMR feature tracking is attracting many CMR users as strain parameters can be relatively easily derived from anyway acquired CMR cine images and recent data suggests that they can help in prognostication (*Figure 7*). Some studies suggested that strain measured might detect SV dysfunction earlier than the measurement of ejection fraction (6,69,70). In addition, global strain measures and

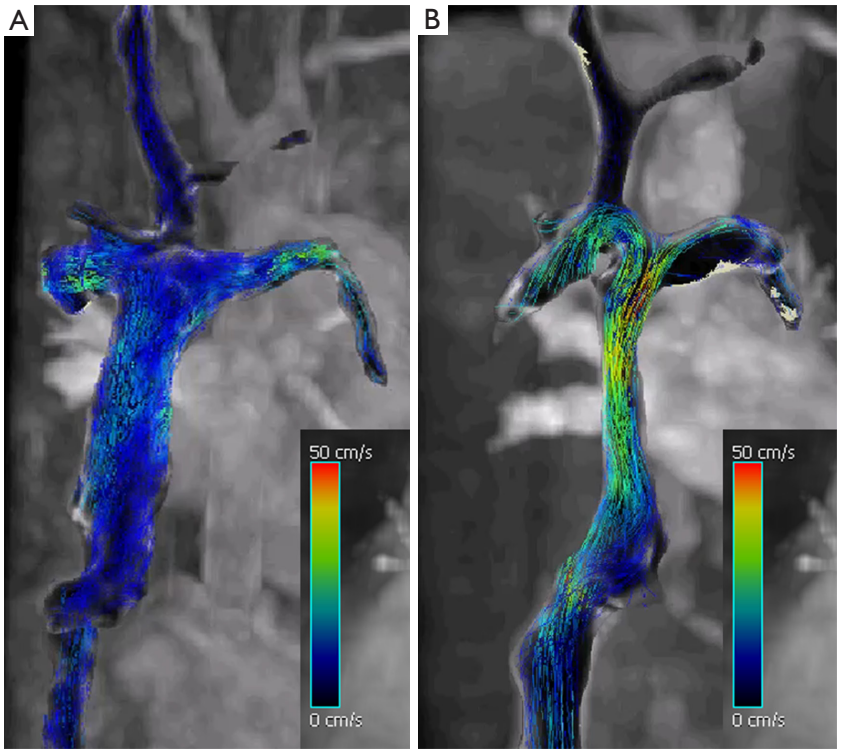

Figure 8 Total cavopulmonary connections with an intraatrial lateral tunnel (A) and a 16 mm extracardiac conduit (B). 4D Flow derived pathlines with colour coding show lower velocity in the intraatrial lateral tunnel (A) compared to the extracardiac conduit (B).

feature tracking-derived dyssynchrony metrics and torsion have also been related to adverse outcome death or need for heart transplantation (5,25,72-74) and subclinical dysfunction (71).

Similar to ventricular function parameters, atrial function can be assessed using volumetry and feature tracking. Few studies indicate that atrial function markers might be helpful for risk prediction, however, further research is needed (26,75).

With the increasing knowledge about Fontan associated lymphatic disorders and ability for interventional treatment, CMR lymphatic imaging is gaining importance. However, there is also expanding evidence that lymphatic imaging might improve prognosis evaluation in Fontan patients. Kelly *et al.* showed that lymphatic abnormalities can progress over time and in their study progression to a high-grade classification was associated with worse postoperative outcomes (14). Other works demonstrated that the degree of lymphatic burden was related with the clinical status, higher liver enzymes and the presence of lymphatic disorders (76-78).

Fontan associated liver disease is a serious complication of the Fontan circulation and common in adult Fontan patients (53). Reasons are not fully understood yet and are likely multifactorial. Recently it became more obvious that small tunnel connections can play an important role (79). CMR studies showed that a smaller cross-sectional area of the inferior vena cava was associated with markers of Fontan associated liver disease (80). 4D Flow can be of use to assess this further (*Figure 8*). Rijnberg *et al.* showed that kinetic energy and energy loss in the total cavopulmonary connection derived from 4D Flow was associated with increased levels of liver fibrosis and congestion (34).

Finally, stress CMR parameters, particularly functional reserve, may be useful for outcome evaluation (81).

Advanced methods—computational-fluid dynamics (CFD) and deep learning

Challenges in long-term outcomes of the patients with SV physiology have motivated the development of hemodynamic models to which CMR can make important contributions by providing data on anatomy, flow boundaries and vascular properties. However, clinical

applications are rare and remain largely unexplored. Several approaches exist for modelling hemodynamics of the Fontan circulation. The most comprehensive approach is the detailed 3D CFD simulation which models details of fluid-dynamics such as power loss and blood flow distributions in order to identify adverse hemodynamic conditions (82-85). The demands of CFD simulations in terms of personnel, technical expertise, computational resources and time expense has hampered the use of patient-specific computational hemodynamics modelling in the routine clinical practise. Several approaches exist based on one- or zero-dimensional ordinary differential equation (ODE) methods as well as lean CFD pipelines that address the problem of time expense (86,87). Zero-dimensional ODE models, often referred to lumped parameter models, contain no space variable and represent a whole circulatory system or a component with its hydraulic impedance (88-90). One-dimensional ODE models simulate directional flow conditions and were used to simulate flow and pulse wave propagation throughout the Fontan circulation (91). Closed-loop models cover the entire Fontan circulation and can combine one-dimensional equations for modelling flow in the large vessels including total cavopulmonary connection (TCPC) with zero-dimensional equations for modelling flow in heart and organs (86,91). In the long-term management of Fontan patients, models with one- or zero-dimensional equations have been applied to predict or prevent adverse outcomes. In order to minimise abdominal complications, the cardiovascular changes induced by creation of a fenestration or hepatic vein exclusion were studied using a closed loop model (91). The impact of atrial fibrillation in the late phase of Fontan was studied using a lumped parameter model (89). In another study using a patient-specific lumped parameter model, the pressure drop in the liver was predicted as a potential parameter for liver health (90). A combined one- and zero-dimensional ODE approach was recently calibrated and validated based on CMR and catheterization data (86). The new model and calibration methodology are freely available and may be adapted to patient-specific boundaries for future prognostic models in adult patients. In addition to one- or zero-dimensional ODE models, the deep-learning based prediction of hemodynamics may be another time-saving approach applicable to SV patients in the future (92). To date, patient-specific computational modelling in univentricular patients has been used mainly for research purposes and has not become an integral part of clinical routine, although potentials have been indicated in several studies (89-91,93,94).

Strengths and limitations

This narrative review provides an overview of recent CMR research in SV patients and gives information about the general use of CMR in Fontan patients. Besides this, gaps in knowledge and limitations of advanced techniques such as that some of them are not implemented into the clinical workflow are described. But the review is not without limitations. First, the field of CMR is evolving constantly and there might be new findings that are not included in this article. Furthermore, the structure and focus of the review might be influenced by subjective factors. Nevertheless, effort has been made to give a comprehensive overview of recent research and developments.

Conclusions

CMR is an essential imaging modality in Fontan patients and is able to provide a detailed overview of the cardiovascular anatomy, function and hemodynamic situation. In addition, increasing knowledge is available about the benefit of magnetic resonance imaging to assess fibrotic changes of the myocardium and to evaluate the lymphatic system. Recent research also focuses on the prognostic role of CMR in Fontan patients and shows that this modality is allowing us to better monitor these complex patients. The increasing portfolio of CMR methods is accompanied by advancements in informatics and fluid mechanics that will likely improve the assessment of Fontan patients and patient cohorts.

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