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ORIGINAL ARTICLE

The trajectory of renal function following mechanical circulatory support and subsequent heart transplantation

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Abstract

Aim Patients with advanced heart failure (HF) frequently suffer from renal insufficiency. The impact of durable mechanical circulatory support (MCS) and subsequent heart transplantation (HTx) on kidney function is not well described.

Methods and results We studied patients with advanced HF who received durable MCS as bridge to transplantation (BTT) and underwent subsequent HTx at our centre between 1996 and 2018. Glomerular filtration rate (GFR) was measured by ^{51}Cr-EDTA or iohexol clearance during heart failure work-up; 3–6 months after MCS; and 1 year after HTx. Chronic kidney disease (CKD) was classified according to KDIGO criteria based on estimated GFR. A total of 88 patients (46 ± 15 years, 84% male) were included, 63% with non-ischaemic heart disease. The median duration of MCS-treatment was 172 (IQR 116–311) days, and 81 subjects were alive 1 year after HTx. Measured GFR increased from 54 ± 19 during HF work-up to 60 ± 16 mL/min/1.73 m^2 after MCS ($P < 0.001$) and displayed a slight but nonsignificant decrease to 57 ± 22 mL/min/1.73 m^2 1 year after HTx ($P = 0.38$). The trajectory of measured GFR did not differ between pulsatile and continuous flow (CF) pumps. Among patients 35–49 years and those who were treated in the most recent era (2012–2018), measured GFR increased following MCS implantation and subsequent HTx. Estimated GFR displayed a similar course as did measured GFR.

Conclusions In patients with advanced heart failure, measured GFR improved after MCS with no difference between pulsatile and CF-pumps. The total study group showed no further increase in GFR following HTx, but in certain subgroups, including patients aged 35–54 years and those treated during the latest era (2012–2018), renal function appeared to improve after transplant.

Keywords Advanced heart failure; Cardiorenal syndrome; Glomerular filtration rate; Mechanical circulatory support; Left ventricular assist device (LVAD); Biventricular assist device (BiVAD)

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Introduction

Patients with advanced heart failure (HF) frequently suffer from renal insufficiency.[1] A reciprocal deterioration of cardiac and kidney function, termed the cardiorenal syndrome (CRS), leads to fluid retention, diuretic resistance, hospital readmission, and impaired survival.[2–6]

Candidates for heart transplantation (HTx) with CRS may receive durable mechanical circulatory support (MCS) as a bridge-to-transplantation (BTT) with the intention to improve renal function. Despite the risk for acute kidney injury, an MCS implantation may facilitate renal function through increased cardiac output and reduced venous congestion.[7–11] However, the increase in glomerular filtration rate (GFR) after MCS observed in different studies[8,12,13] does not appear to be sustained over time. Whether newer continuous flow devices may affect kidney function differently than do older pulsatile systems is under debate.[13–15]

The development of renal dysfunction after heart transplantation (HTx) is common and multifactorial. According to the International Society for Heart and Lung Transplantation (ISHLT), the presence of irreversible renal dysfunction conforming GFR $<$ 30 mL/min/1.73 m^2 is a relative contraindication for HTx.[16]

Previous studies on how MCS and HTx may affect renal function have used estimated GFR (eGFR), which is based on formulas including the serum or plasma concentration of creatinine as well as the patient's age, sex, and weight.[17] The gold standard for assessing renal function is the direct measurement of GFR (measured GFR; mGFR) by the plasma clearance of either ^{51}Cr-ethylenediamine tetraacetic acid (EDTA) or iohexol. However, these methods are seldom applied being labour-intensive and costly.[18,19]

In the present study of patients with advanced HF, we used both measured and estimated GFR to investigate how renal function is affected by treatment with a durable MCS and subsequent HTx.

Methods

Patient population

All patients who were treated with durable MCS as BTT and underwent subsequent HTx at Sahlgrenska University Hospital between 1996 and 2018 were screened for the study (n = 116). Patients younger than 16 years (n = 16), subjects treated with MCS less than 30 days and individuals with missing GFR data (n = 12) were excluded from the study, resulting in 88 patients in total. Among those, 41 had pulsatile pumps and 47 continuous flow (CF) pumps. A flow chart illustrating patient inclusion is depicted in the Supporting Information, *Figure S1*. Of the 88 study patients at baseline, a total of 81 (92%) were alive 1 year after HTx. The study complies with the Declaration of Helsinki and the study protocol was approved by the Swedish Ethical Review Board (D-nr 728-12, 2020-04281).

In Sweden, implantation of MCS as destination therapy (DT) is not yet approved, which explains why all our pump implants were BTT, and in a few cases bridge-to-candidacy. The outcome of patients treated with LVAD as compared with DT is now being investigated in a national randomized trial,[20] but participants of this trial were not included in the present study.

Data extraction

A retrospective chart review was performed in order to analyse characteristics of all patients identified by the electronic search. Anthropometric and clinical characteristics [age, gender, body mass index (BMI), and New York Heart Association (NYHA) class] were extracted for each patient. Data from laboratory examinations, echocardiography, and right heart catheterization were also collected. Blood samples obtained were analysed by the Central Laboratory of Sahlgrenska University Hospital (accredited according to the European Norm 45.001).

Assessment of renal function

Glomerular filtration rate was measured by the plasma clearance of ^{51}Cr-EDTA or iohexol (mGFR, mL/min/1.73 m^2) at three time points: (i) during heart failure work-up; (ii) 3 to 6 months after implantation of a durable MCS; and (iii) at 1 year follow-up after HTx. In case several measurements were performed, the one closest to the intervention, whether it was MCS implantation or HTx, was chosen. In patients who died before 1 year follow-up after HTx, data from the first two time points were used when available. The ^{51}Cr-EDTA and iohexol methods were considered to be equivalent, because these procedures have previously been shown to be interchangeable.[21] At the same three timepoints, the severity of chronic kidney disease (CKD) was classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria (5 stages) based on the level of GFR estimated by the Modification of Diet in Renal Disease (MDRD) formula as follows: GFR = 175 × (creatinine/88.4)$^{-1.154}$ × (age)$^{-0.203}$ (if female: × 0.742). The choice of the MDRD was based on clinical practice and data suggesting that the MDRD performed better than the Cockcroft–Gault equation when evaluating eGFR in a HTx population.[22]

Surgical procedures

The MCS systems were implanted through a median sternotomy on cardiopulmonary bypass after heparinization (ACT $>$480 seconds). The Heartmate 1 and Novacor pumping chambers were placed intraabdominally, whereas the Berlin Heart EXCOR pumping houses were located para-corporeally, that is, outside of the body. All continuous flow MCS-systems were placed intrathoracically, with the driveline tunnelled subcutaneously to an exit cite on the abdominal wall. After implantation, the MCS pumping rate was commenced and augmented in a slow stepwise manner, until the patient could be weaned from cardiopulmonary bypass. As soon as the patient became haemodynamically stable and displayed a satisfactory haemostatic balance, the sternotomy was closed in a regular fashion and the patient was transferred to intensive-care unit.

Heart transplantation was performed via a re-sternotomy on cardiopulmonary bypass after heparinization. After cross-clamping the ascending aorta, the heart with the adjoining MCS-system was explanted and a donor heart implanted applying the standard bicaval technique. In the

beginning, transplantations in patients with intrathoracic pumps were complicated by a cumbersome pump explanation with diffuse bleeding due the presence of adhesions. This issue with adhesions was solved later on by wrapping a GoreTex-membrane around the pump at the time of implantation, which facilitated subsequent explanation and, thereby, simplified the transplantation procedure and reduced the risk of bleeding.

Types of mechanical circulatory support

Due to a continuous development of durable MCS during a prolonged inclusion time (22 years), our study included several different pump systems. The population treated with pulsatile pumps received both left ventricular assist devices (LVADs) and biventricular assist devices (BiVADs) (Supporting Information, *Figure S1*). The pulsatile devices included Heart Mate I (n = 12), Novacor (n = 2), Berlin Heart Excor (n = 25), and Syncardia TAH (n = 2), and the continuous flow devices used in this study were Ventrassist (n = 4), DeBakey (n = 7), Heartware (n = 1), Heart Mate II (n = 28), and Heart Mate 3 (n = 7). During the period 1996–2004, most LVADs were pulsatile, whereas after the year 2005, continuous flow devices became standard LVAD treatment. Seven patients died before the first annual control after HTx (three from the first period of implantation and four from the second and none from the third). No patients were lost to follow up.

Immunosuppression after heart transplantation

The immunosuppression protocol included induction therapy with anti-thymocyte globulin and maintenance therapy with a calcineurin inhibitor, CNI (cyclosporine before 2004, either cyclosporine or tacrolimus 2005–2011, tacrolimus after 2011), an antimetabolite (azathioprine replaced by mycophonalate mofetil during 2002) and a corticosteroid, which was tapered during the first year after HTx. In 2005, we adopted a protocol including everolimus and low-dose CNI in selected patients, including those with CNI side-effects, deteriorating renal function, coronary artery vasculopathy, or cancer.

Of the 81 patients (92%) who survived until 1 year follow-up after HTx, 80 patients were treated with a CNI, 21 were on everolimus along with low dose CNI, and 1 patient was treated with a CNI free regimen (everolimus, mycophenolate mofetil, and corticosteroids).

Statistical methods

All statistical analyses were performed using the R statistical software packages (R Core Team, 2021). Descriptive statistics are presented as mean ± standard deviation (SD) or medians and interquartile ranges for continuous variables, and as numbers with percentages in parentheses for categorical variables. All patients with at least one measurement of GFR were included in the analysis of renal function over time.

Both the total study population, as well as sub-groups based on whether individuals treated with a pulsatile or continuous flow pump, age categories ($<$35 years, 35–54 years, and $>$55 years) and three different periods of implantation (1996–2004, 2005–2011 and 2012–2018) were studied. Statistical comparisons between groups were performed with an unpaired t-test for normally distributed data, Mann–Whitney U-test, or Kruskal–Wallis test for nonparametric data and Fischer's exact test for categorical data.

Within-patient change in mGFR and eGFR was assessed using within-patient t-test with Bonferroni–Holm adjusted P-values. Furthermore, mean mGFR level was explored by analysing repeated measurements using a mixed model including, age category, MCS-type, period of implantation and visit as main effects and MCS-type*visit, age*visit, and period*visit as interaction terms, subjects were included as random with a compound symmetry correlation structure. Least square means were presented with nominal 95% confidence intervals and P-values.

Results

Patient characteristics

Baseline demographics, medical history, and preoperative laboratory values by device type are displayed in *Table 1*. Patients treated with pulsatile flow pumps were younger, more often female, had less frequently hypertension, and had lower haemoglobin compared with those with CF pumps. Dilated cardiomyopathy was the most common cause of heart failure in both groups. There were no differences in creatinine or eGFR between patients treated with pulsatile versus CF pumps.

New York Heart Association functional class, preoperative echocardiographic data, invasive haemodynamic measurements, need for inotropic treatment, and ventilatory support are shown in *Table 2*. Patients with pulsatile pumps tended to have lower functional capacity than those with CF pumps, but the difference was not significant (P = 0.09) Left ventricular ejection fraction (EF) and left ventricular end diastolic diameter (LVEDD) were similar in both groups. Patients receiving pulsatile flow pumps had higher right atrial pressure (P = 0.01) and tended to have lower cardiac index (P = 0.08). Otherwise, the haemodynamic variables were similar in the two groups, and there were no group differences with respect to inotropic treatment or ventilatory support. The distribution of patients between different age groups and periods of MCS-implantation is shown in the Supporting Information, *Table S1*.

Table 1 Demographics, medical history, and pre-operative laboratory values

	Total (n = 88)	Pulsatile (n = 41)	Continuous (n = 47)	P-value
Demographics				
Age (years)	46 ± 15	40 ± 13	50 ± 14	<0.001
Male sex	74 (84)	31 (76)	43 (92)	0.042
Body mass index (kg/m^2)	26 ± 4	25 ± 4	27 ± 4	0.037
Body surface area (m^2)	2.0 ± 0.3	2.0 ± 0.3	2.0 ± 0.2	0.482
Medical history				
Previous hypertension	10 (12)	0 (0)	10 (23)	0.001
Diabetes	8 (9)	3 (7)	5 (11)	0.591
Previous cardiac surgery	16 (18)	8 (19)	8 (17)	0.843
Aetiology of heart failure				0.144
Dilated cardiomyopathy	55 (63)	30 (73)	25 (54)	
Ischaemic heart disease	22 (25)	5 (13)	17 (36)	
Congenital heart disease	3 (3)	1 (2)	2 (4)	
Myocarditis/inflammatory heart disease	3 (3)	2 (5)	1 (2)	
Hypertrophic/restrictive CMP	1 (1)	1 (2)	0 (0)	
Other	4 (5)	2 (5)	2 (4)	
Laboratory values				
Haemoglobin (g/L)	122 ± 21	117 ± 22	126 ± 19	0.040
Bilirubin (μmol/L)	15 (9; 25)	15 (8; 25)	14 (9; 24)	0.563
NT-proBNP	3255 (1560; 6727)	4090 (2333; 9283)	3170 (1055; 6184)	0.237
Creatinine (μmol/L)	127 ± 55	127 ± 61	126 ± 50	0.941
eGFR (MDRD) and CKD stage				
eGFR (mL/min)	63 ± 24	61 ± 23	64 ± 24	0.591
Stage 1 (>90)	14 (16)	4 (10)	10 (21)	
Stage 2 (60–89)	30 (34)	17 (42)	13 (28)	
Stage 3 (30–59)	41 (47)	18 (44)	23 (49)	
Stage 4 (15–29)	3 (3)	2 (4)	1 (2)	

Values are presented as means ± SD, numbers (%), or medians (interquartile range).
CKD, chronic kidney disease; CMP, cardiomyopathy; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Table 2 Pre-operative functional capacity (NYHA), echocardiography measurements, haemodynamic profiles, and need for inotropic and/or ventilatory support

	Total (n = 88)	Pulsatile (n = 41)	Continuous (n = 47)	P-value
Clinical heart failure severity				
NYHA functional class IIIB–IV versus II–IIIA	79 (90)	40 (98)	39 (83)	0.09
Echocardiographic measurements				
Left ventricular end diastolic diameter (cm)	7.2 ± 1.3	7.4 ± 1.5	7.0 ± 1.2	0.23
Left ventricular ejection fraction (%)	21 ± 9	20 ± 5	23 ± 11	0.21
Invasive haemodynamic measurements				
Heart rate (b.p.m.)	82 ± 23	83 ± 25	82 ± 21	0.85
Right atrial pressure (mmHg)	10 ± 6	12 ± 6	9 ± 6	0.01
Mean pulmonary artery pressure (mmHg)	31 ± 13	29 ± 11	31 ± 14	0.52
Pulmonary capillary wedge pressure (mmHg)	20 ± 9	21 ± 8	20 ± 9	0.67
Mean arterial blood pressure (mmHg)	66 ± 18	65 ± 19	67 ± 16	0.62
Cardiac index (L/min/m^2)	2.1 ± 0.8	1.8 ± 0.5	2.2 ± 0.9	0.08
SvO_2 (%)	57 ± 12	53 ± 11	58 ± 12	0.13
Circulatory and ventilatory support				
Intravenous inotropic therapy	33 (38)	19 (45)	14 (30)	0.15
Mechanical ventilation	5 (6)	3 (7)	2 (4)	0.55

Values are presented as means ± standard deviations, or numbers and percentages within parentheses.
SvO_2, mixed venous oxygen saturation.

Perioperative events

Data on perioperative events in association with HTx for different time eras are shown in *Table 3*. Time on heart-lung machine was shorter during the first era as compared with the second and third era. Organ ischaemic time, reoperation for bleeding, need for continuous renal replacement therapy, days in the intensive care unit (ICU), days in hospital, and reoperations did not differ between different time periods.

Renal function

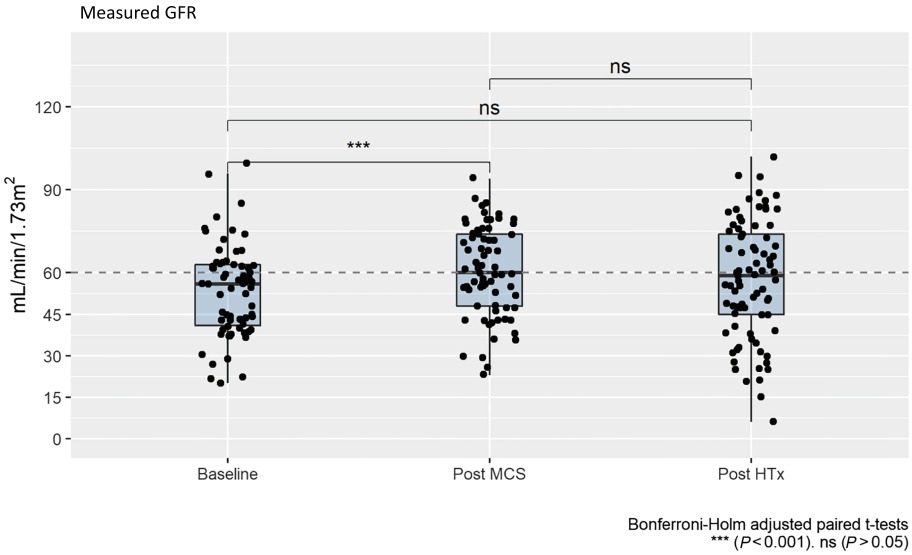
Figure 1 displays the distribution of mGFR at each measurement point. mGFR by age categories and implantation

Table 3 Perioperative and postoperative factors and events in association with HTx for different time periods

	Total (n = 88)	1996–2004 (n = 14)	2005–2011 (n = 33)	2012–2018 (n = 41)	P-value
ECC-time (min)	164 (141;199)	139 (118;177)	173 (160;210)	162 (142;192)	0.002
Donor heart ischaemia time (min)	188 (127;228)	174 (149; 191)	189 (133; 239)	192 (117; 227)	0.45
Time in the ICU (days)	6 (3;11)	3.5 (3;7)	7 (3;15)	6 (4;11)	0.36
Time in hospital (days)	31 (27;42)	32 (28;42)	31 (30;46)	28 (26;40)	0.33
Complications, *n* (%)					
Reoperation due to bleeding	24 (27)	4 (29)	9 (27)	11 (26)	0.99
CRRT in the ICU	26 (30)	3 (21)	12 (36)	11 (26)	0.57

Values are presented as medians and interquartile ranges or numbers and percentages within parentheses.
CRRT, continuous renal replacement therapy; ECC, extracorporeal circulation; HTx, heart transplantation; ICU, intensive care unit.

Figure 1 Individual mGFR by measurement point. mGFR at baseline, after implantation of MCS, and at 1 year follow up after HTx. Filled circles indicate individual measurements. Median, Q1 and Q3 are displayed in boxes. mGFR, measured glomerular filtration rate; MCS, mechanical circulatory support; HTx, heart transplantation.



periods in are shown in the Supporting Information, *Figure S2A,B*. Mean measured GFR increased significantly from 54 ± 19 to 60 ± 16 mL/min/1.73 m^2 after implantation of MCS (mean within patient change +8.3, 95% CI 4.1 to 12.6, $P < 0.001$). At 1 year after HTx, the mean mGFR had again decreased to 57 ± 21 mL/min/1.73 m^2, but this was not statistically significant (mean within patient change –3.1, 95% CI 1.6 to −7.8, P = 0.38), *Figure 1*.

In the adjusted model, the mGFR showed the same marginal mean increase and decrease after MCS and after HTx (mean change from baseline to after MCS + 6.1; 95% CI 0.9 to 11, P = 0.02).

Figure 2 presents the change in mean mGFR by type of device. No significant difference was seen between continuous and pulsatile implants when adjusting for age and period of implantation. *Figure 3A,B* presents the change in mean mGFR by age category and period of implantation. For the age cohorts, there was a significant increase between baseline and after HTx in patients 35–54 years (+8.4 mL/min/1.73 m^2; 95% CI 0.1 to 17, P = 0.04), whereas no significant changes over time were observed for other age categories (*Figure 3A*). For implantation periods, patients from the first era (1996–2004) showed a continuous decrease in mGFR from baseline to after HTx (−18 mL/min/1.73 m^2; 95% CI −33 to −2.9, P = 0.01), whereas patients from the third period of implantation (2012–2018) displayed a continuous increase in mGFR from baseline to after HTx (+7.6 mL/min/1.73 m^2; 95% CI 2.4 to 15, P = 0.04). In patients from the second era (2005–2011), mGFR increased after MCS (+12 mL/min/1.73 m^2; 95% CI 3.8 to 20, P = 0.002) and then decreased again after HTx (−8.9 mL/min/1.73 m^2; 95% CI −17 to −2.6, P = 0.03) (*Figure 3B*).

All patients had available baseline creatinine measurements for calculation of estimated GFR. The proportion of patients in CKD-stage 1–2 (vs. 3–4) increased from 50% at baseline to 79% after treatment with MCS (P = 0.008). At

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Figure 2 Adjusted mean mGFR in patients with continuous and pulsatile flow pumps. Mean mGFR at baseline, after implantation of MCS, and at 1 year follow up after HTx in patients with continuous and pulsatile pumps (after adjustment for age category and period of implantation). Error bars presenting 95% confidence intervals. Brackets show significant changes. mGFR, measured glomerular filtration rate, MCS, mechanical circulatory support; HTx, heart transplantation.

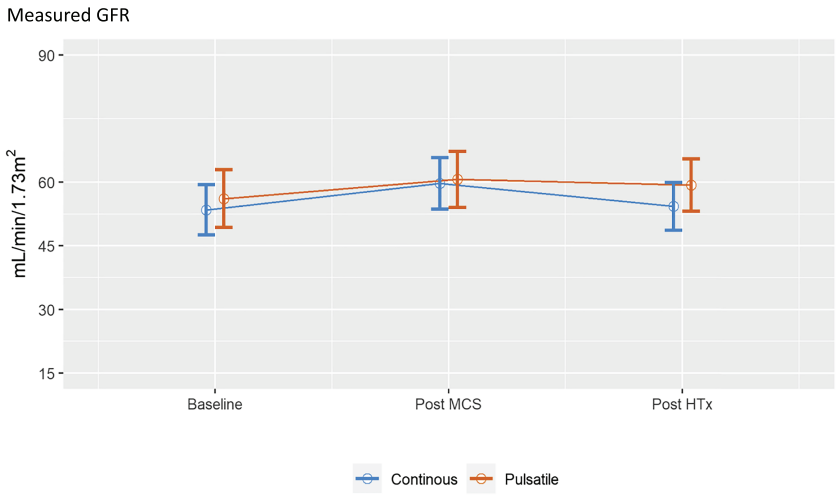
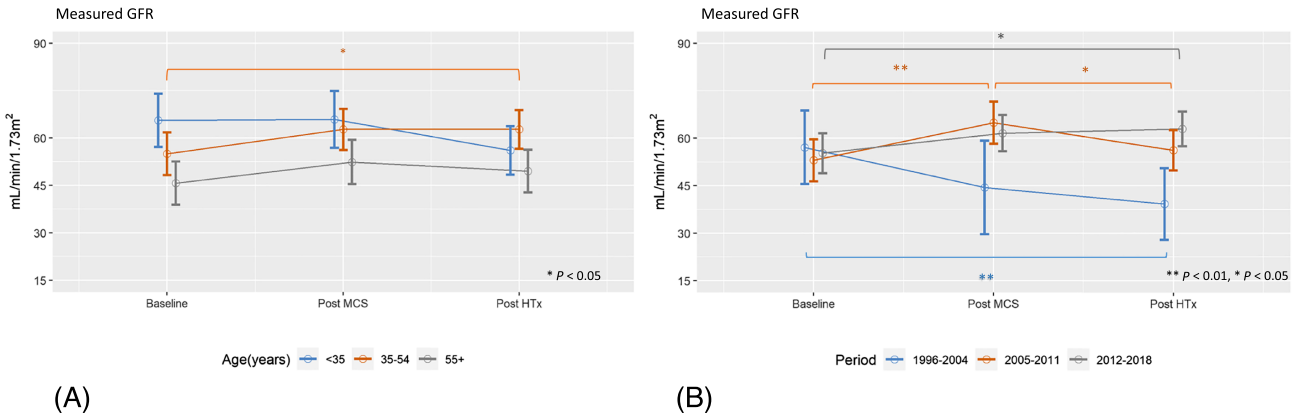


Figure 3 Adjusted mean mGFR by age categories and periods of implantation. Mean mGFR at baseline, after implantation of MCS, and at 1 year follow up after HTx in patients by different age categories (after adjustment for MCS-type and period of implantation) (A) and by period of implantation after adjustment for MCS-type and age category (B). Error bars presenting 95% confidence intervals and brackets show significant changes. mGFR, measured glomerular filtration rate; MCS, mechanical circulatory support; HTx, heart transplantation.



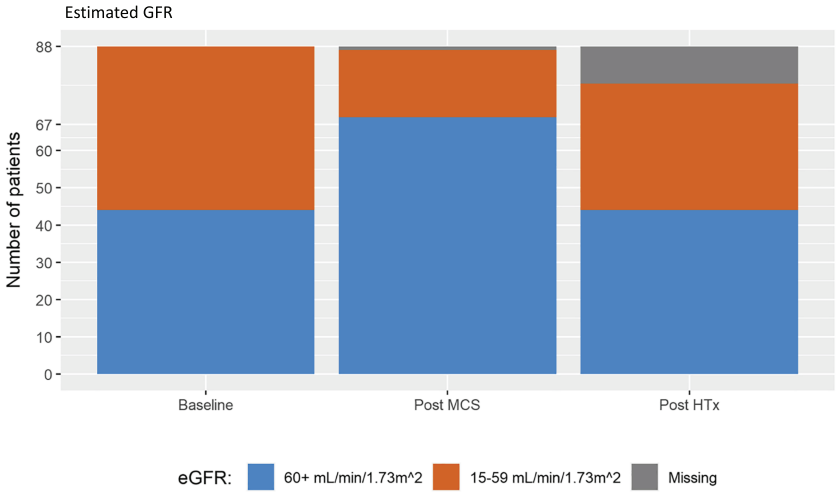
1 year after HTx, the proportion had again decreased to 56% (P = 0.02) (*Figure 4*). Changes in eGFR are shown in the Supporting Information, *Table S2* and the exact numbers and proportions of patients in CKD-stage 1–2 versus 3–4 at the three time points in the Supporting Information, *Table S3*.

Discussion

In the present study, among patients with advanced heart failure, measured GFR increased after 3–6-month treatment with MCS. The total study group showed no further increment at 1 year follow-up after HTx. However, in certain subgroups including patients aged 35–54 years and among those treated during the latest era (2012–2018), measured GFR increased following MCS implantation and subsequent HTx. The trajectory of mGFR did not differ between subjects treated with pulsatile pumps and those managed with continuous flow pumps.

Patients with advanced heart failure frequently suffer from the cardiorenal syndrome, which is associated with increased morbidity and mortality.[2,3] Poor renal function, along with advanced age and BMI, is the most common contraindications

Figure 4 CKD-stages by measurement point. Number of patients in CKD stage 1–2 (eGFR > 60 mL/min/1.73 m^2) and stage 3–4 (eGFR 15–59 mL/min/1.73 m^2) at baseline, after implantation of MCS, and at 1 year follow up after HTx. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MCS, mechanical circulatory support; HTx, heart transplantation.



to HTx.[23] Previous studies have shown that treatment with durable MCS may improve renal function, assessed as creatinine or estimated GFR,[7–10,24] but estimated GFR tends to decline again over time. One explanation may be that reduced muscle mass early after surgery reflected by low creatinine levels causes overestimation of GFR. The increase in muscle mass during the next months, thereafter, may cause higher creatinine levels and a reduction in estimated GFR without representing actual changes in kidney function.

An important novelty of the present study is that we used measured GFR to study the impact of MCS implantation on renal function and, thereby, avoided the effect of muscle mass on GFR. A previous study showed none of the Cockcroft–Gault, MDRD, or CKD-EPI equations estimated GFR particularly well in patients before or after HTx.[25] The correlations between the three GFR estimates and mGFR were, at most, moderately high at any time point, indicating that mGFR, when available, should be preferred in such clinical situations. Correct estimation of renal function is of great importance when it comes to decision making following work up for MCS and HTx.

Our findings that measured GFR increases after MCS implantation are in line with earlier observations with estimated GFR. However, because we only had one measurement during MCS treatment, we were not able to study longitudinal changes during treatment on pump. Improvements in renal function following MCS implantation are likely due to renal decongestion and improved renal blood flow. Apart from haemodynamic mechanisms, a reduction in neurohormonal activity is likely to facilitate renal microvascular function and autoregulation.[26]

In previous studies, improvements in estimated GFR after MCS are transient with eGFR returning to pre-MCS levels in the majority of patients within 1 year.[12] The question has been raised whether older pulsatile pumps may be more advantageous with respect to renal function as compared with newer continuous flow systems.[13–15] In the present study, after adjusting for age and period of implantation, measured GFR did not differ between subjects treated with pulsatile and continuous flow pumps. Still, it should be noted that patients with a pulsatile pump during the two latest eras most often had received the device in a form of a BiVAD due to significant biventricular failure and, thereby, differed clinically at baseline from patients treated with continuous flow pumps who had more suitable right ventricular function. Nonetheless, patient outcomes at our centre have been similar for the two groups, as is previously reported.[27] Sandner *et al*. have also observed comparable effects on renal function assessed by eGFR for pulsatile and continuous flow pumps, respectively.[9,15] Thus, pulsatile flow does not appear to be crucial for renal function, but further studies are needed to explain the drop in GFR during treatment with durable MCS.

The stagnation of or tendency towards impaired measured GFR levels after HTx was not entirely unexpected. In a previous publication from our group, we found a mean drop in mGFR of 12% during the first year after HTx as compared with the preoperative value.[28] A vast majority of our MCS patients were transplanted from a relatively stable clinical situation, but there are several other factors that may have a negative influence on renal function. These include the presence of renal insufficiency previous to the operation, acute kidney injury related to the surgical procedure and the introduction of nephrotoxic calcineurin inhibitors afterwards.[29,30] Still, the distribution of mGFR increased following HTx (*Figure 1*), implying increments in mGFR among certain subgroups and

impairment among others, but with a mean value slightly lower than that observed after MCS.

In the subgroup of middle-aged subjects (35–49 years), measured GFR increased following MCS implantation and subsequent HTx. We speculate that this age group had the greatest potential to reverse the cardiorenal syndrome and improve measured GFR following MCS and HTx. This differed from younger subjects (<35 years) for which the mGFR tended to decline after treatment with MCS and HTx. A possible explanation is that younger subjects started from a higher mGFR level offering less potential to improve. Furthermore, individuals in this age category are likely to receive a more aggressive immunosuppressive therapy due to a higher inclination to organ rejection. Older patients (≥55 years), which started from a lower mGFR, remained quite stable during treatment with MCS and HTx. We hypothesize that this subgroup, due to a higher age, had a more limited capacity to reclaim lost renal function. Our findings are of clinical relevance when evaluating patients different age groups with advanced HF for BTT.

Among patients treated during the latest era (2012–2018) measured GFR increased following MCS implantation and subsequent HTx. On the contrary, subjects managed during the first era (1996–2004) displayed a continuous decline in mGFR. Thus, the trajectory of renal function following advanced HF treatment appears to be improving over time. We observed no differences in organ ischaemic time, reoperations for bleeding, renal replacement therapy, time in the intensive care unit, or time in hospital after HTx between the different eras. Time on heart-lung machine was somewhat shorter during the first era as compared with the second and third era. Thus, we hypothesize that better renal function in the latest era could be related to other factors including development of donor management, more experienced surgeons and improved post-operative care. Furthermore, optimization of immunosuppressive treatment including renal sparing protocols comprising everolimus and low dose CNI is also likely to preserve GFR and contribute to improved renal function in the most recent era. On the other hand, we feel that the use of antibiotics in connection with MCS treatment is unlikely to have influenced our results. In a previous study, which included patients treated with either LVAD (n = 21) or BiVAD (n = 20), only 5–15%[27] were in need for treatment with an i.v. antibiotic, and the percentage that required antibiotics during the entire HTx wait time was considerably lower.

Due to the length of our study, immunosuppression changed between the three time periods. The trough levels targeted for CNIs were also somewhat lower during the most recent period. After 2005, we adopted a renal sparing regimen for selected cases with renal insufficiency. In these patients, everolimus was added and CNI-doses were reduced with approximately 50%.

When using eGFR, we observed the same trajectory as for mGFR following MCS implantation and subsequent HTx. Our findings were in line with previous publications in which estimated GFR was applied as an assessment for renal function.[8,10,15,31] The majority of patients in CKD-stage 3–4 (66%) improved to stage 1–2 after MCS. This is clinically relevant because it confirms that much of the improvement is seen in patients with reduced renal function at baseline. It also raises the concern of not waiting too long with LVAD implantation in order to achieve improvement of kidney function after MCS. After HTx, the GFR declined again almost reaching the baseline values. However, due to low muscle mass, the assessment of GFR at baseline and after MCS could be overestimated, especially in younger patients. Similarly, the decrease in eGFR at 1 year follow-up after HTx could in part be related to increased muscle mass.

The main strength of our study is the availability of measured GFR considered to be gold standard in determining renal function and that no patients were lost to follow-up. Conversely, the observational, retrospective nature of the study is an important limitation with respect to the degree of evidence we can provide. Further, the study population was heterogeneous and treated with various types of MCS devices during a long study period. Also, a relatively small sample size and missing values regarding mGFR reduce the statistical power and constrain our conclusions. Finally, detailed knowledge of the duration and course of pre-operative renal dysfunction was not available to our analysis and might have caused bias with respect to the subsequent trajectory of kidney function.

Conclusion

Assessment of renal function is of utmost importance when evaluating patients with advanced heart failure for durable MCS and/or HTx. For this purpose, most centres apply estimated GFR which is less reliable than measured GFR. In the present study, we used measured GFR, which increased after treatment with a durable MCS, with no differences between pulsatile and continuous flow pumps. When analysing mGFR for the total study group, no further increase in measured GFR was observed following HTx. However, in certain subgroups including those between 35–54 years of age and those treated during the latest era (2012–2018) the trajectory of renal function appeared to improve. This suggests advancement over time, probably consisting of improved HTx procedures and immunosuppressive protocols that are benevolent for renal function.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow diagram of patients who received MCS as bridge to transplantation (BTT) and underwent subsequent HTx at Sahlgrenska University Hospital during the study period.

Figure S2. Individual mGFR by measurement point in different age categories and implantation periods.

Legend: mGFR at baseline, after implantation of MCS and at 1-year follow up after HTx in patients by the different age categories (A) and implantation periods (B). Filled circles indicate individual measurements. Median, Q1 and Q3 are displayed in boxes. *mGFR* = measured glomerular filtration rate, *MCS* = mechanical circulatory support, *HTx* = heart transplantation.

Table S1. Distribution of age categories and periods of MCS-implantation in the study population.

Table S2. Change of eGFR (MDRD) between measurements during the study.

Table S3. Shift from baseline CKD stage (eGFR, MDRD).

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