

# A Systematic Review of Renal Functional Reserve in Adult Living Kidney Donors



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**Introduction:** The kidney's capacity to increase its glomerular filtration rate (GFR) in response to a higher functional demand is known as the renal functional reserve (RFR). Good short-term outcomes after living kidney donation have led to more acceptance of borderline donors (with hypertension, obesity, older age) due the ongoing shortage of donor organs. Given recent concerns about increased long-term risk in some donor subgroups, better donor stratification is needed. Measurement of RFR could inform assessment of donor risk.

**Methods:** A systematic literature review of studies that assessed RFR in donors pre- and/or post-donation was performed. Given study heterogeneity, descriptive analysis and narrative synthesis was conducted.

**Results:** Sixteen of 3250 identified studies published between 1956 and 2019 met inclusion criteria. Most studies were cross-sectional and conducted before ( $n = 8$ ) and/or after ( $n = 16$ ) kidney donation. Methods for measurement of GFR, effective renal plasma flow (ERPF) and RFR were not standardized. Changes in filtration fraction (FF) and ERPF relative to GFR observed after donation varied depending on stimulus used to induce RFR. Overall, RFR fell after donation; however, over the shorter term, RFR was largely preserved in young healthy donors. RFR was more significantly reduced in donors with hypertension, obesity, or older age.

**Conclusion:** Existing data suggest possible blunting of RFR post-donation in older, obese, and hypertensive donors, which may represent increased single-nephron GFR at baseline. The long-term implications of these changes deserve further study to determine utility in informing selection of borderline kidney donors.

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**KEYWORDS:** borderline kidney donors; glomerular filtration rate; kidney function; living kidney donation; nephron; renal functional reserve

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Kidney transplantation confers a better quality of life and better survival compared with dialysis and is more cost-effective over the long-term.<sup>1</sup> Living kidney donation presents an important source of organs given the shortage of deceased donor kidneys. Growing confidence, based on satisfactory short- and long-term outcomes in living kidney donors (LKDs), has led to the inclusion of more borderline donors (i.e., older age, controlled hypertension, low-grade proteinuria, body mass index [BMI] up to 35).<sup>2</sup> In addition, the final decision of the transplant nephrologist in living donor selection is still highly dependent

on estimated GFR, which is, however, not an ideal method to determine actual kidney function given the known factors affecting its accuracy (e.g., protein intake, muscle mass, physical activity, age, sex). Recent studies have highlighted poorer long-term outcomes in certain donor populations, such as those of African American or indigenous origin and obese donors.<sup>3–5</sup> As all donors are generally well screened before donation, routine clinical parameters alone (blood pressure, urine protein, kidney function, body mass/size at the time of donation) have not been robust predictors of long-term risk in such donor populations.<sup>5</sup> Final acceptance of a living donor is, however, still highly dependent on GFR, which may be affected by multiple nonrenal factors (e.g., protein intake, muscle mass, physical activity, age, gender), and which when estimated, tends to underestimate measured GFR in LKDs.<sup>6,7</sup>

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After nephrectomy, the single kidney undergoes an adaptive increase in function of approximately 35%.<sup>5,8,9</sup> This capacity of a kidney to increase its GFR when there is a higher functional demand is recognized as the renal functional reserve (RFR).<sup>10</sup> Experimental data on 11 of 12 nephrectomies in rats indicate that hyperfiltration driven by glomerular hypertension leads to progressive kidney failure.<sup>11,12</sup> How relevant these data are in the case of a 50% loss of nephron mass in healthy LKDs is not clear given the general long-term safety of living kidney donation; however, this paradigm may be more applicable to borderline kidney donors.

Static measurement of GFR does not capture RFR or whether the single-nephron GFR (SNGFR) is already elevated at baseline (i.e., already using the RFR for baseline function). Measurement of RFR (most commonly induced by protein or amino acid loading or dopamine infusion) can be considered a renal *stress test*, which can assist in determining whether a kidney has the capacity to increase its baseline function or not.<sup>9</sup> Such information could inform decisions on whether donation of a kidney in an individual donor would be acceptable or not, within the context of other risk factors, and may be useful in prospective studies to determine whether the pre-donation RFR can predict stability of long-term kidney function post-donation in borderline candidates. Although RFR testing has been established for decades and makes physiologic sense, it has not entered into routine clinical practice, in part because it is cumbersome and in part because the true clinical impact and utility have not been rigorously studied.<sup>9</sup> Challenges in extrapolating results across different methodologies and simultaneous inclusion of diverse patient groups has also likely hampered understanding and interpretation of studies on RFR. Given the increasing need for organs and the practice of accepting more borderline donors, there is an obligation for the kidney transplant community to develop tools to better predict the longer-term risk in potential donors.

We conducted a systematic review of studies that measured RFR in LKDs, to describe patterns in higher-risk donor subgroups before and after kidney donation, and to investigate potential associations with long-term kidney function. The underlying aim of the study was to better understand the potential clinical value of RFR measurement in borderline kidney donors, and thus its utility in informing donor selection.

## METHODS

### Search Strategy and Selection Criteria

A systematic literature review was performed based on the Preferred Reporting Items for Systematic Reviews

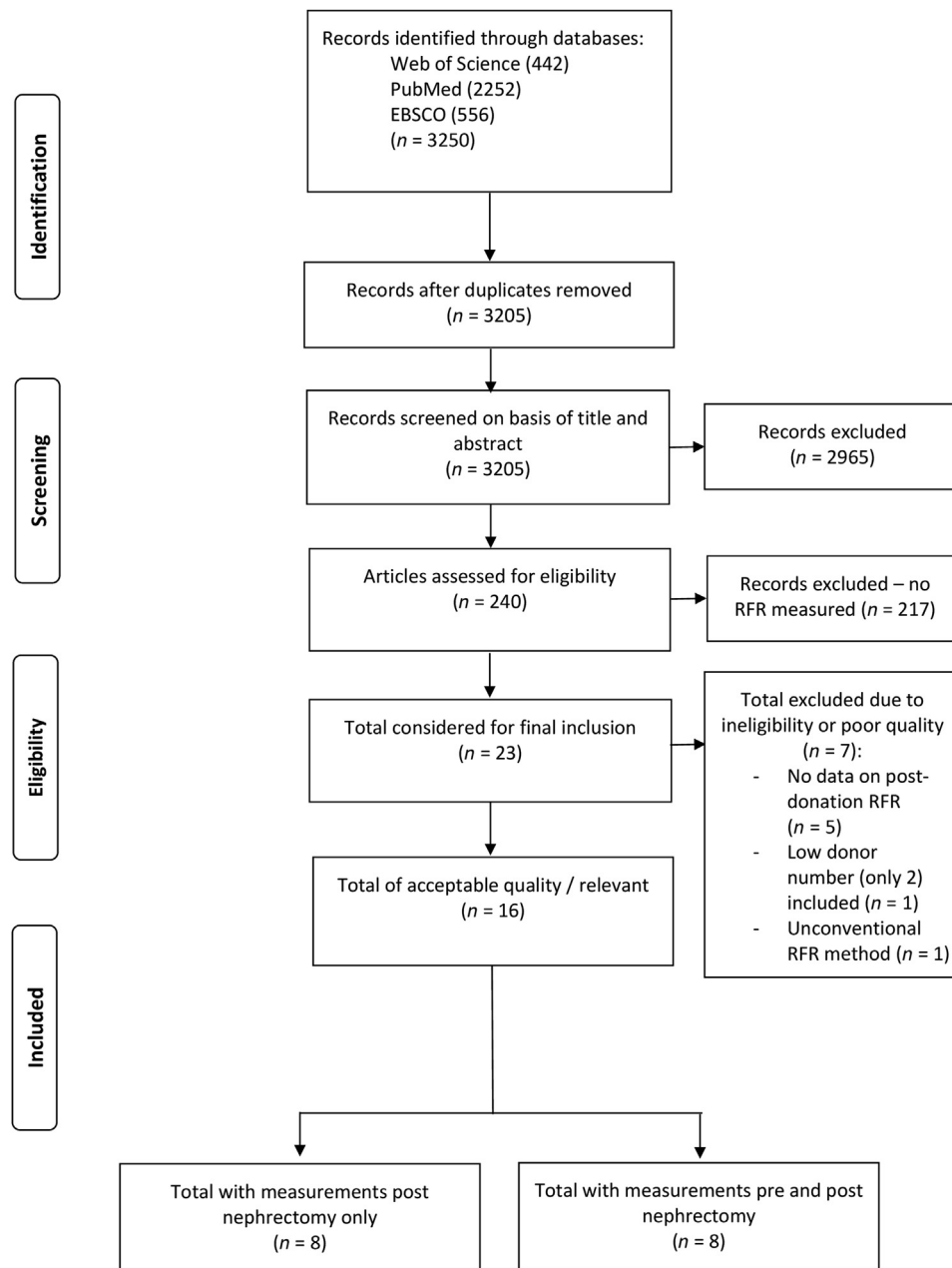
and Meta-Analysis (PRISMA) guidelines.<sup>13</sup> PubMed, EBSCO, and Web of Science were searched from January 1, 1956, up to January 26, 2019, using the following search terms: *kidney function glomerular filtration rate OR renal functional reserve capacity OR renal blood flow AND kidney donor (PubMed), kidney function glomerular filtration rate AND renal functional reserve capacity OR renal blood flow AND kidney donor (EBSCO, Web of Science)*. Studies were restricted to the English language and were included for analysis if they reported RFR in living donors both before and/or after kidney donation. Studies that did not evaluate post-donation RFR were excluded, as they did not permit assessment of RFR in the remaining kidney after living kidney donation. Studies also were excluded if performed in animals and in recipients of deceased donor organs. Two authors (VAL and AF) independently screened titles and abstracts and studies fulfilling inclusion criteria were analyzed in full text.

### Quality Assessment and Data Extraction

Study quality was assessed independently by 2 authors (VAL and AF) using the Critical Appraisal Skills Programme (CASP) checklist for case-control studies.<sup>14</sup> Studies were considered of low quality if measurement of RFR did not use an established method (section A), precision of RFR test method was questionable with wide variability in low subject numbers (section B), or the results may not have been generalizable (section C). Minor disagreements were discussed and a consensus achieved in discussion with author TM. Studies were deemed of low quality if RFR measurements were not standardized and/or results were highly variable across small subject numbers or included subjects not likely to be representative of the larger donor group. Data from studies meeting acceptable quality (e.g., inclusion of detailed methodology used for GFR and RFR measurements, as well as analyzing potential confounding factors) and inclusion criteria were extracted into Microsoft Excel. AF performed initial data extraction, which was verified independently by VL and TM.

### Data Analysis

Given the heterogeneity of studies with regard to study population, method of measurement of RFR and timing of testing pre- and post-kidney donation, a descriptive analysis with narrative synthesis was performed. Pre- and post-donation data in the same subjects were analyzed in 8 studies. Post-donation RFR was analyzed in all 16 studies. RFR findings were stratified by donor characteristics (age, sex, BMI) where described. Data on long-term kidney function (>5 years post-donation) were extracted when reported.



**Figure 1.** PRISMA flow diagram. RFR, renal functional reserve.

## RESULTS

A total of 3250 studies were identified through the literature search terms (Figure 1). Of these, 23 studies were considered for final analysis. Five studies were excluded because they did not measure RFR post-donation, 2 were excluded for low quality, 1 of which included only 2 living donors, and 1 that used an unconventional method to measure RFR, results were highly variable and a minority of eligible patients were included. Sixteen studies therefore fulfilled the inclusion criteria. All studies reported RFR measurement post-donation, 8 studies included both pre- and post-donation measurements (Table 1<sup>15–29</sup>). In total,

RFR measurements were reported for 1547 donors, whereas both pre- and post-donation data were available for 1425 donors.

### Methods Used to Assess GFR and ERPF

Methods used for GFR and RFR measurements with changes in GFR, ERPF, RFR, and FF are presented in Table 1. Six studies<sup>15–20</sup> assessed GFR using creatinine clearance, all before or including 1986, and 11 studies used exogenous marker clearance, from 1986 onward. One study used both creatinine and inulin clearance.<sup>16</sup> Radiolabeled iothalamate was used in 8 studies,<sup>21–28</sup> and diethylenetriamine pentaacetic acid was used in 1

**Table 1.** RFR studies with data pre- and post-donation

Study	Subject no.	Donor groups	GFR measurement	ERPF measurement	RFR method (stimulus)	Dosage	Time pre/post (mo)	Pre-donation GFR baseline/ stimulated (ml/min)	Post-donation GFR baseline/ stimulated (ml/min)	Pre-donation ERPF baseline/ stimulated (ml/min)	Post-donation ERPF baseline/ stimulated (ml/min)	Pre-donation FF baseline/ stimulated (%)	Post-donation FF baseline/ stimulated (%)	RFR GFR pre/post (%)	RFR ERPF pre/post (%)
van Londen, 2018 <sup>26</sup>	937	All	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine	1.5 µg/kg per min	4/3	114/124	72/75	378/450	256/291	31/28	29/26	9/3	19/14
	383	Subgroup with long-term data					4/5.1 yr	116/126	78/ND	407/496	263/ND	29/25	30/ND	9/ND	22/ND
van Londen, 2018 <sup>27</sup>	105	Female donors	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine	1.5 µg/kg per min	4/2	118/128	76/80	405/496	286/322	30/26	27/25	8/5	22/11
Tent, 2012 <sup>25</sup>	47	Hypertensive	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine	1.5 µg/kg per min	4/2	118/128	73/74	419/514	267/305	29/25	28/24	8/1	23/14
	94	Normotensive						113/122	70/72	406/498	263/298	28/24	27/24	8/3	23/13
Rook, 2008 <sup>28</sup>	178	All	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine	1.5 µg/kg per min	4/2	114/126	72/76	—	—	—	—	11/5	—
ter Wee, 1994 <sup>23</sup>	15	Long-term data	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine AA Dopamine + AA	1.5–2 µg/kg per min 500ml/6h	—/4.9 yr	NA/NA	78/84 <sup>o</sup> 78/86 <sup>o</sup> 78/92 <sup>o</sup>	NA/NA	303 <sup>o</sup> /382 <sup>o</sup> 303 <sup>o</sup> /322 <sup>o</sup> 303 <sup>o</sup> /397 <sup>o</sup>	NA/NA	26/22 26/27 26/23	NA/8 NA/10 NA/18	NA/26 NA/6 NA/31
	(12)	Subgroup with short-term data			Dopamine + AA	1.5–2 µg/kg per min 500ml/6h	—/1.3	111 <sup>o</sup> /DG	69 <sup>o</sup> /DG	426 <sup>o</sup> /DG	290	26/—	24/—	DG	DG
ter Wee, 1990 <sup>21</sup>	20	All	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine AA Dopamine + AA	1.5–2 µg/kg per min 500ml/6h	—/8–73 d	107 <sup>o</sup> /121 <sup>o</sup> 107 <sup>o</sup> /120 <sup>o</sup> 107 <sup>o</sup> /1320 <sup>o</sup>	67 <sup>o</sup> /71 <sup>o</sup> 67 <sup>o</sup> /73 <sup>o</sup> 67 <sup>o</sup> /78 <sup>o</sup>	417 <sup>o</sup> /550 <sup>o</sup> 417 <sup>o</sup> /460 <sup>o</sup> 417 <sup>o</sup> /584 <sup>o</sup>	277 <sup>o</sup> /332 <sup>o</sup> 277 <sup>o</sup> /294 <sup>o</sup> 277 <sup>o</sup> /346 <sup>o</sup>	26/22 26/26 26/23	24/21 24/25 24/23	13/6 12/9 23/16	32/20 10/6 40/25
ter Wee, 1987 <sup>22</sup>	10	All	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine	1.5–2 µg/kg per min	—/3	114 <sup>o</sup> /129 <sup>o</sup>	68/72 <sup>o</sup>	441 <sup>o</sup> /600 <sup>o</sup>	274 <sup>o</sup> /344 <sup>o</sup>	26/21	25/21	13/6	36/26
Chan, 1986 <sup>19</sup>	10	All	Creatinine	—	Oral protein	60 g	—/6	119/134	77/84	—	—	—	—	13/9	—
ter Wee, 1986 <sup>24</sup>	14	All	<sup>125</sup> I-iothalamate	<sup>131</sup> I-hippurate	Dopamine	1.5–2 µg/kg per min	—/—	—/—	76 <sup>o</sup> /82 <sup>o</sup>	—/—	308 <sup>o</sup> /376 <sup>o</sup>	—/—	25/22	—/8	—/22
Herrera, 1998 <sup>16</sup>	7	All	Inulin Creatinine	—	Oral protein	80 g	—/1–72	—/—/—	77 <sup>o</sup> /87 <sup>o</sup> 98 <sup>o</sup> /119 <sup>o</sup>	—	—	—	—	—/13 —/21	—
Englund, 1997 <sup>30</sup>	15	All	Inulin	PAH	Oral protein	1.5 g/kg	—/4.8 (median)	—/—	72 <sup>o</sup> /86 <sup>o</sup>	—/—	366 <sup>o</sup> /436 <sup>o</sup>	—/—	20/19	—/20	—/20
Loo, 1994 <sup>17</sup>	12	All	Creatinine	—	Oral protein	100 g	—/ND	—/—	66 <sup>o</sup> /72 <sup>o</sup>	—	—	—	—	—/8	—
Tapson, 1986 <sup>20</sup>	28	All	Creatinine	—	Oral protein	80 g	—/13–262	—/—	79 <sup>o</sup> /98 <sup>o</sup>	—	—	—	—	—/25	—
Rodriguez, 1985 <sup>15</sup>	25	All	Creatinine	—	Oral protein	100–150 g	—/12–132	—/—	115 <sup>o</sup> /137 <sup>o</sup>	—	—	—	—	—/19	—
Cassidy, 1988 <sup>18</sup>	12	All	Creatinine	—	Oral protein	1.2 g/kg	—/36–120	117/—	78/96	—	—	—	—	—/23	—
George, 1996 <sup>29</sup>	9	All	DTPA	—	Oral protein	1.2 g/kg	—/1	96 <sup>o</sup> /—	56 <sup>o</sup> /55 <sup>o</sup>	—	—	—	—	—/—1	—

AA, amino acid; DG, data presented only as a graph, numbers not extractable; DTPA, diethylenetriamine pentaacetic acid; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; NA, not applicable; ND, not done; PAH, paraaminohippurate; RFR, renal functional response.

<sup>o</sup>GFR normalized for body surface area (ml/min per 1.73 m<sup>2</sup>).

study.<sup>29</sup> Inulin, gold standard for GFR measurement, was used only in 2 studies.<sup>16,30</sup> Overall, the measured GFR levels before and after donation were similar across the studies, creatinine clearance-based values were slightly higher than iothalamate measurements, and all indicated a fall in GFR of 35% (range, 33%–42%) from pre- to post-donation. ERPF was measured in 9 studies by using radiolabeled hippurate infusion<sup>21–28</sup> or para-aminohippurate.<sup>30</sup> ERPF levels before and after donation were in a similar range across the studies, corresponding with the 35% fall in GFR, indicating no overall change in FF from pre- to post-donation (range, 29%–38%).

### Stimuli Used to Induce Renal Functional Reserve

Oral protein loading, either containing a fixed amount of protein (60–150 g) or adjusted according to donor body weight (1–1.2 g/kg), i.v. dopamine, amino acids (AAs), or dopamine with AAs were variably used to elicit the RFR across studies. Trends of the differential physiologic effects of these substances on GFR and renal perfusion are summarized in Table 2.<sup>15–30</sup> Overall, dopamine infusions appear to induce the RFR through an increase in ERPF, relatively greater than the increase in GFR, indication of a fall in FF. I.v. AA or oral protein loading, in contrast, were associated with a greater effect on GFR relative to ERPF, indicating an increase in FF. The greatest effect on RFR was observed with co-administration of dopamine and AA, which increased GFR and ERPF in parallel. RFR protocols used in the studies are summarized in Table 3.<sup>15–30</sup>

### Determination of RFR

RFR was measured 4 months before donation in 4 of 8 studies, all done by the same group and following the same protocol. Timing of RFR measurement pre-donation in the remaining 4 studies was not reported. The intervals between kidney donation and post-donation RFR measurements were variable across the 16 studies, as shown in Table 1, ranging from 1 month to 22 years. RFR is reported as the percent increase in baseline GFR on stimulation of kidney function. The percent change in post-donation RFR across studies was variable, which could be partly explained by the use of different methodologies for GFR measurement and for GFR stimulation. Studies in which GFR was measured by creatinine clearance showed higher RFR (range, 8%–25%) when compared with those in which clearance of an exogenous marker was used (range, 4%–8%) (Table 1).

Overall, the comparison between RFR pre- and post-donation (8 studies) indicates that post-donation RFR is reduced compared with the pre-donation (range,

12.5% up to 75.0% decrease from pre-donation value). These studies predominantly used dopamine stimulation. The use of protein or AA was associated with greater increases in RFR after donation (ranges 8%–25% for protein; 9%–10% for AA, and 16%–18% for AA + dopamine). Overall, the RFR is variably reduced post-donation and may be modulated by donor age, BMI, and sex. In some donors, RFR was preserved post-donation (Table 4<sup>15,18,28</sup>).

### Donor Age and RFR

Three studies evaluated the impact of donor age at time of kidney donation on RFR (Table 4). Rook *et al.*<sup>28</sup> included pre- and post-donation data. Using <sup>125</sup>I-iothalamate to measure GFR and i.v. dopamine as a stimulus, this group showed that RFR at 2 months post-donation was best preserved in the age group 21 to 45 years and showed a significant decline in subjects 54 to 75 years of age, not seen with the pre-donation RFR (Table 4). Rodriguez *et al.*<sup>15</sup> and Cassidy and Beck<sup>18</sup> tested the RFR long-term after donation. They applied similar cutoff age levels and measured post-donation RFR only, using creatinine clearances and oral protein loading. In these studies, RFR was relatively preserved over the long-term; however, selection bias cannot be excluded, as patient numbers were extremely small. The oldest donors were aged 60 years compared with 75 years in the larger study by Rook *et al.*<sup>28</sup> Overall, older age may blunt the RFR post-donation, suggesting some utilization of renal functional reserve at baseline. However, more long-term data on renal functional adaptation and RFR are needed to assess the impact of age on long-term kidney function post-donation. Data regarding ERPF and FF were not available in these studies, limiting analysis and conclusions.

### Donor Weight and RFR

Two studies<sup>26,28</sup> analyzed the effect of BMI on RFR before and after donation (Table 5<sup>27,28</sup>). Both studies used <sup>125</sup>I-iothalamate for GFR measurement and dopamine to induce the RFR. Overweight donors had higher GFRs pre- and post-donation compared with normal-weight donors, suggesting increase in SNGFR due to body size and higher metabolic demand, although no difference was observed in post-donation albuminuria.<sup>26,28</sup> Donors with BMIs of  $\geq 25$  kg/m<sup>2</sup> had a significantly greater decline in RFR post-donation compared with those with BMI <25 kg/m<sup>2</sup>, measured at 2 months post-donation (Table 5). BMI correlated inversely with post-donation RFR. In both studies, the loss of RFR associated with nephrectomy was already seen in relatively young donors (mean age between 41 and 52 years) with only a mild degree of obesity (BMI

**Table 2.** Stimulation methods for RFR testing and their physiological importance

Stimulating agent	Effect on GFR	Effect on ERPF	Effect on FF	Effect on RFR (GFR)
Dopamine, i.v.	↑ 8%–13% pre-donation 1%–8% post-donation	↑↑ 19%–36% pre-donation 13%–26% post-donation	↓ –10% to –19% pre-donation –7% to –16% post-donation	↑ 8%–13% pre-donation 1%–8% post-donation
AA, i.v.	↑↑ 12% pre-donation 9%–10% post-donation	↑ 10% pre-donation 6% post-donation	↑/ ↔ 0% pre-donation 4% post-donation	↑↑ 12% pre-donation 9%–10% post-donation
Dopamine + AA, i.v.	↑↑↑ 23% pre-donation 16%–18% post-donation	↑↑↑ 40% pre-donation 31% post-donation	↔ –12% pre-donation –4% to –12% post-donation	↑↑↑ 23% pre-donation 16%–18% post-donation
Oral protein	↑↑↑ 13% pre-donation 9%–24% post-donation (–2% <sup>o</sup> )	↑↑ 19% post-donation	↑/ ↔ –5% post-donation	↑↑/ ↑↑↑ 13% pre-donation 8%–25% post-donation (–1% <sup>o</sup> )

↑, increase; ↑↑, higher increase; ↑↑↑, highest increase; ↓, decrease; ↔, no change; AA, amino acid; ERPF, effective renal plasma flow; FF, filtration fraction; GFR, glomerular filtration rate; RFR, renal functional response.

<sup>o</sup>Based on 1 study (George et al.<sup>23</sup>).

Compiled from the following studies: Rodriguez-Iturbe et al.,<sup>15</sup> Herrera et al.,<sup>16</sup> Loo et al.,<sup>17</sup> Cassidy and Beck,<sup>18</sup> Chan,<sup>19</sup> Tapson et al.,<sup>20</sup> ter Wee et al.,<sup>21–24</sup> Tent et al.,<sup>25</sup> van Londen et al.,<sup>26,27</sup> Rook et al.,<sup>28</sup> George et al.,<sup>29</sup> and Englund et al.<sup>30</sup>

>25). The early study time point 2 to 3 months post-donation in both studies does not permit conclusions regarding the long-term implications.

### Donor Sex and RFR

Two studies examined the impact of sex on post-donation RFR (Supplementary Table S1). Tapson et al.<sup>20</sup> and Cassidy and Beck,<sup>18</sup> using change in creatinine clearance after an oral protein load, found that female donors (40–54 years) may have a marginally higher RFR post-donation compared with male donors (40–55 years) at 1 to 22 years after donation (26% vs. 24% and 32% vs. 14%, respectively). Given the heterogeneity in these 2 studies, there is not enough data to support potential differences in RFR after kidney donation between male and female kidney donors.

### Donor Hypertension and RFR

Tent et al.<sup>25</sup> examined the change in RFR at 4 months pre- and 2 months post-donation in hypertensive donors using <sup>125</sup>I-iothalamate and i.v. dopamine (Table 1). RFR was not different (8% vs. 8% of baseline GFR) in hypertensive and normotensive donors pre-donation,

but after kidney donation, RFR was lower in both hypertensive and normotensive donors (1% vs. 3% of baseline GFR). ERPF and FF were higher in hypertensive donors both pre- and post-donation. Blood pressure and renal function were similar in hypertensive donors and controls at all time points. Given the small differences in RFR and FF and the short period of follow-up, conclusions as to the long-term impact of donation on RFR and kidney function in hypertensive donors cannot be drawn.

### RFR Over the Long-term

There were no longitudinal studies comparing pre- and long-term post-donation data on RFR. The largest study with 5-year follow-up data on kidney function in 383 donors did not measure RFR post-donation.<sup>26</sup> A few studies that measured only post-donation RFR after 5 years or longer indicate a retained reserve capacity; however, the numbers of subjects included are very small, selection bias cannot be excluded (i.e., those who did well), and pre-donation measurements for comparison are not available (Table 1).<sup>15,18,20,23,30</sup>

**Table 3.** Protocols for renal functional reserve testing in living kidney donors

Marker	Preparation	Initial hydration	Maintenance hydration	Stimulus	Clearance time	Number of clearances pre/post	Advantages	Disadvantages
Inulin	Standard diet	20 ml/kg	5–10 ml/kg or equal to urinary output	Oral protein in 30 min	30 min	3/4–6	Gold standard for GFR measurement, usually measured together with ERPF	Costs, need for infusion, more blood sampling in short period, possible allergic reactions
iothalamate	Standard diet	Together with radiopharmaceutical infusion	100–200 ml/h	Dopamine and/or amino acid at constant rate infusion	2 h	1/1	Reliable GFR measurement, usually measured together with ERPF	Continuous infusion, often need for 2 venous lines, possible allergic reactions
Creatinine	7–10 days protein low diet	20 ml/kg to 1000 ml	250–300 ml or equal to urinary output	Oral protein in 30 min	30 min to 2 h	1–3/1–8	Low costs, no allergic reactions, simple method	Results affected by tubular secretion, muscle mass, more blood sampling in short period

ERPF, effective renal plasma flow; GFR, glomerular filtration rate.

Compiled from Rodriguez-Iturbe et al.,<sup>15</sup> Herrera et al.,<sup>16</sup> Loo et al.,<sup>17</sup> Cassidy and Beck,<sup>18</sup> Chan,<sup>19</sup> Tapson et al.,<sup>20</sup> ter Wee et al.,<sup>21–24</sup> Tent et al.,<sup>25</sup> van Londen et al.,<sup>26,27</sup> Rook et al.,<sup>28</sup> George et al.,<sup>29</sup> and Englund et al.

**Table 4.** RFR according to age of living donors (at time of kidney donation)

Study	Patient no.	Age (yr)	GFR measurement	RFR method (stimulus)	Dosage	RFR GFR pre (%)	RFR GFR post (%)
Rook, 2008 <sup>28</sup>	62	21–45	<sup>125</sup> I-iothalamate	Dopamine	1.5 µg/kg per min	10	8
	59	46–53				12	7
	57	54–75				10	3
Rodriguez, 1985 <sup>15</sup>	8	20–30	Creatinine	Oral protein	100–150 g	NA	30
	9	31–40				NA	24
	8	41–60				NA	2
Cassidy, 1988 <sup>18</sup>	1	<30	Creatinine	Oral protein	1.2 g/kg	NA	–3
	6	30–40				NA	25
	5	40–60				NA	24

GFR, glomerular filtration rate; NA, not available; post, post-donor nephrectomy; pre, pre-donor nephrectomy; RFR, renal functional response.

### Blood Pressure and Urine Protein Post-Donation

Cassidy and Beck<sup>18</sup> found an increase in proteinuria 3 to 10 years post-donation (297 mg/24 hours compared with 106 mg/24 hours pre-donation), but there was no confirmed association between RFR and albuminuria post-donation. In contrast, Tent *et al.*<sup>25</sup> found no significant proteinuria at 2 months and 5 years after donation in hypertensive or healthy donors; however, albuminuria was not available. Hypertensive donors had higher pre- and post-donation GFR compared with nonhypertensive donors (118 ml/min vs. 113 ml/min and 73 ml/min vs. 70 ml/min, respectively).<sup>25</sup> Mean arterial pressures remained stable over 5 years in both hypertensive and nonhypertensive donors.<sup>25</sup>

## DISCUSSION

Analysis of RFR before and after living kidney donation suggests that RFR is reduced after kidney donation, and the reduction is relatively greater among older, overweight, and possibly hypertensive donors. The heterogeneity of methods used, the timing of measurements, the overall small donor numbers, the predominantly cross-sectional analyses, and most important the lack of long-term data across the studies limit comparison of findings and do not permit robust conclusions regarding the value of RFR in informing decision making for living kidney donation.

Donor safety, in particular long-term sufficient renal function, is the key requirement in LKD organ transplantation. Thorough donor evaluation and knowledge

about long-term consequences of uninephrectomy, especially in borderline candidates, is therefore extremely important. Post-donation healthy kidneys increase their GFR by approximately 35%.<sup>8</sup> Brenner and colleagues<sup>11,12</sup> demonstrated that a major loss of nephron mass induces hyperfiltration, which when driven by glomerular hypertension leads to progressive nephrosclerosis and kidney failure. This key paradigm in nephrology questions safety and acceptability of living kidney donation, a procedure characterized by a loss of 50% of nephrons and an adaptive increase in SNGFR. Living donation has, however, appeared generally safe over the long-term, although recent studies have highlighted a minor but significant risk for end-stage kidney disease in LKDs when compared with adequately matched healthy controls, especially among certain subgroups, such as African American individuals and those with elevated BMI.<sup>5,31–33</sup> Given that more borderline candidates are being considered for kidney donation, their risks of kidney dysfunction over time may also prove to be increased. Better risk-stratification pre-donation could inform the challenging discussions with potential donors where there is often inherent tension between not doing harm, the limits of altruism, and respecting autonomy. Theoretically, RFR measurement could provide such relevant information.

The adaptive increase in SNGFR after kidney donation occurs due to hemodynamic and structural changes of the remaining glomeruli.<sup>34</sup> Because the increase in filtration of the single nephron uses reserve capacity to a certain degree, it may be expected that

**Table 5.** RFR according to BMI of living donors (at time of kidney donation)

Study	Patient no.	Age (yr)	BMI (kg/m <sup>2</sup> )	GFR pre (ml/min)	GFR post (ml/min)	Albuminuria pre (g/l)	Albuminuria post (g/l)	RFR GFR pre (%)	RFR GFR post (%)
van Londen, 2018 <sup>27</sup>	54	41	<25	112	70	1.0	2.3	9	9
	51	41	≥25	125	82	1.5	2.3	8	2
Rook, 2008 <sup>28</sup>	87	46	<25	111	70	NA	NA	11	7
	70	49	25–30	117	74	NA	NA	11	5
	21	52	>30	119	74	NA	NA	11	1

BMI, body mass index; GFR, glomerular filtration rate; NA, not available; pre, pre-donor nephrectomy; post, post-donor nephrectomy; RFR, renal functional response.

with the loss of a significant amount of nephron mass (post-donation) the remaining RFR will be lower. Indeed, a higher baseline GFR pre-donation was already seen in hypertensive and obese donors compared with those without hypertension and non-obese donors, suggesting the presence of hyperfiltration, which may explain the observed tendency toward a dampened RFR post-donation.<sup>25,27</sup> A loss of RFR was also seen in older donors,<sup>26,28</sup> again suggesting elevated SNGFR and a possible exhaustion of reserve capacity at baseline. The question of the long-term consequence of the loss of RFR and the mechanism by which this increase in filtration is sustained cannot be answered by the existing studies. This circumstance could plausibly lead to more rapid progressive loss of kidney function in the face of superimposed stress.<sup>35</sup>

Longitudinal measurements of GFR and ERPF allowing for calculations of FF would permit discrimination of hemodynamic functional changes from structural changes. It would be most interesting, especially in borderline donors, to know whether a long-term increase in SNGFR is sustained primarily by maladaptive glomerular hypertension with possible stress on the filtration barrier, or by glomerular hypertrophy without significant changes in FF and pressure gradients. Recent publications point toward *benign* glomerular enlargement and adaptive hyperfiltration with hyperperfusion and enlargement of the filtration surface area in some donors.<sup>34,36–38</sup> However, these elegant functional and morphometric studies were performed in healthy, predominantly Caucasian donors without functional testing of RFR and only after a medium-term follow-up period.

There is currently no ideal method to test RFR or for clinical assessment of nephron mass. Ideal tests should be robust, safe, easy to perform, and inexpensive, making them feasible to perform in the clinical routine. Clinically, GFR is usually estimated rather than measured. Obstacles to measurements of GFR with the gold standard method of inulin clearance include cost, time, availability, and potential allergic reactions. Comparable obstacles apply for alternative exogenous markers (e.g., radiolabeled iohalamate, iohexol, diethylenetriamine pentaacetic acid, EDTA), which also require radiation exposure. Many RFR studies therefore have used the clearance of endogenous creatinine instead,<sup>15,17,20,39</sup> despite the fact that creatinine is not only filtered but also secreted and thus estimates of GFR and urine collections are subject to error. Herrera *et al.*<sup>16</sup> simultaneously measured inulin and creatinine clearance before and after a protein meal. They showed that both clearance methods detect a protein-induced increase in GFR. The inulin and creatinine clearance values correlated well for the baseline conditions

(pre-meal). The stimulated clearance (post-meal) was relatively higher using the creatinine- compared with the inulin-based method in healthy subjects, however, likely due to the increase in tubular creatinine secretion. This effect was not seen in subjects with chronic kidney disease who might have lost their tubular reserve capacity.<sup>28</sup> Creatinine-based measurement may therefore be subject to inherent variability and is reliant on the adequacy of voided urine samples.

The most frequently used method to elicit the RFR has been dopamine stimulation and <sup>125</sup>I-iothalamate to measure GFR.<sup>21–28</sup> Van Londen *et al.*,<sup>26</sup> using this method, suggested that the pre-donation RFR is not predictive of donor kidney function at 5 years and therefore is *not useful*. This conclusion may be valid as an aggregate; however, those studied at 5 years represented only 40% of the initial cohort and the donors included in this study would generally be considered low risk, having a mean age of 52 ± 11 years, mean BMI of 26 ± 4, a mean systolic blood pressure of 127 ± 13, a prevalence of albuminuria of 3%, and were largely Caucasian. In addition, dopamine alone may not be the best stimulus to reflect full RFR and 5-year follow-up is not long enough to determine kidney life and disease progression.<sup>40,41</sup>

The physiologic increase in GFR after a protein load has long been recognized.<sup>42</sup> The peak GFR in healthy humans is reached approximately 90 minutes after ingestion.<sup>43,44</sup> Good hydration and a resting state are important for detection of this rise in GFR. When comparing other stimuli used to induce the RFR, it has been shown that AA infusions increase GFR more than dopamine infusions, and both given together further increase GFR (Tables 1 and 2). The greater loss of RFR post-donation when using dopamine as a stimulus compared with AA indicates different mechanisms of induction of an increase in filtration and different capacities to elicit maximal SNGFR. The best method to induce and measure RFR and the potential to predict long-term kidney function post-donation remains unknown. New techniques for GFR measurement (e.g., use of visible fluorescent injectate: rhodamine derivative and fluorescein carboxymethylated dextran)<sup>45</sup> could make RFR testing easier and more accessible.

Standardized studies to answer these questions need to be long-term, measure baseline and stimulated filtration as well as renal blood flow before and at regular intervals post-donation, use a robust exogenous GFR marker, stimulate filtration with a significant protein load (>1 g/kg body weight) rather than inducing minor hemodynamic changes via dopamine, focus on borderline patients with changes expected to be detectable in the medium- to long-term, and include subjects with diverse origins from multiple centers.



The predictive value of the pre-donation RFR in more marginal donors with higher ages, blood pressures, and BMIs and of different ethnicities is not known. The few studies reviewed here suggest that older, obese, and hypertensive donors may have a relative loss of RFR post-donation and therefore may be at risk of long-term renal functional decline (Tables 4 and 5).<sup>15,18,26,28</sup>

This increased risk may be amplified in the face of subsequent renal *hits*, such as development of diabetes, worsening blood pressure, increasing weight, or possibly an episode of acute kidney injury.<sup>8</sup> Furthermore, the impact of donor birth weight or prematurity, which are associated with nephron number, on RFR has also not been studied.<sup>46,47</sup> Subjects with low birth weight are at risk of developing hypertension and chronic kidney disease due to increased SNGFR with their already lower nephron number.<sup>48</sup> Small studies have shown that donors with lower birth weights have higher risks of developing hypertension, proteinuria, and lower estimated GFR up to 60 months after nephrectomy.<sup>49,50</sup> As aging may be accelerated in subjects born with low birth weights or preterm, especially if they develop subsequent overweight or obesity, determination of RFR in such a potential donor may be clinically relevant.<sup>47</sup>

Women tend to have fewer nephrons than men, and as yet unexplained, chronic kidney disease, but not ESKD, in general is more prevalent among women.<sup>47</sup> Whether the RFR is different between female and male donors remains unknown. Only 2 studies compared RFR post-donation between a small number of male and female donors without showing significant differences (Supplementary Table S1). Knowledge of the RFR in a female donor may be especially relevant for those who may still be planning a pregnancy or who may be obese (both hyperfiltration states), as the loss of RFR could contribute to hypertension, pre-eclampsia, proteinuria, and worsening of the kidney function during pregnancy, which are known to be more common among female kidney donors.<sup>51,52</sup>

The major strength of this systematic review is that to the best of our knowledge we have included all studies reporting post-kidney donation measurement of RFR. Stratification of studies by method is useful to inform future study design and study interpretation given the differing physiologic effects of the various methods of stimulation. The small number of studies, their cross-sectional nature, and the lack of long-term follow-up, and lack of ethnic diversity are major limitations here, which prevents true understanding of the value of RFR in prediction of long-term function in living donors. This weakness, however, is in itself a strength, as it strongly highlights the need for good

prospective studies going forward. Given that studies have tended to be performed by the same research groups, it is possible that some studies have overlapping patient populations. Given that we have not pooled data, have restricted our analysis to a narrative review, and have stratified the findings by donor category, the potential for overlap has been reduced or eliminated (Tables 4 and 5 and Supplementary Table S1).

Despite the priority of donor safety and hence the need for in-depth functional assessment of living donor kidneys pre- and post-donation, very few studies were identified that measured GFR, ERPF, and RFR over the past 6 decades. The existing data indicate a loss of RFR in borderline donor candidates (i.e., older, hypertensive, or overweight donors). However, long-term data are needed to understand the relevance of these findings, and more specifically to identify the threshold RFR below which donation may not be safe in each of the borderline clinical states. Based on the existing uncertainties, physiologic plausibility, and potential to enhance safety of living donation, we suggest that RFR testing should be further evaluated as a tool to complement the assessment of borderline LKDs.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

**PRISMA Checklist.**

**Table S1.** Studies on RFR according to gender of living donors.

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