Renal Functional Reserve -RFR-

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OUTLINE

• Definition and evaluation of Renal Functional Reserve (RFR);

• Potential applications of RFR: from physiology to pathology;

• Novara-UPO experience in Living Donor Kidney Transplantation (LDKTx).
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RFR is the difference between the stress (peak) GFR achieved by stimulation and the baseline GFR.

RFR identifies the capacity of the kidney to compensate or increase its function in states of demand or disease. Peak GFR can reach up to 180 ml/min in case of an intact nephron mass. It is reduced to approximately 120 ml/min in case of a solitary kidney (50% of nephron mass). In both cases, baseline GFR can result normal, but while RFR is intact in the 1st case, it is virtually zero in the 2nd case.
Comparison of stressors in the heart and kidney.
Kidney stress tests
Urinary output in response to furosemide stress test.

The FST in subjects with early AKI serves as a novel assessment of tubular function with robust predictive capacity to identify those patients with severe and progressive AKI.
NGAL deficiency protects from the progression toward CKD
Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

Kidney stress tests

Renal Functional Reserve
- RFR
Baseline and stress GFR empirically measured in different conditions.
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Summary of renal hemodynamic and metabolic adaptations to normal human pregnancy

Lenght of both kidneys increase by 1 cm

Dilatation of calicyeal system, renal pelvis and ureters

GFR and renal blood flow increase by 30-45% 

Crs fall to 0.4-0.8 mg/dl so Crs of 1 mg/dl in pregnant should be considered as abnormal value

Excretion of glucose, protein and bicarbonate increase during pregnancy
Effect of age on total kidney, cortical and medullar volumes

- There is a rising prevalence of nephrosclerosis with aging, from 2.7% for healthy individuals younger than 29 years up to 73% for healthy individuals over age 70 years.

- Total kidney volume remains stable through about age 50 years due to declining cortical volume and a compensatory medullary volume increase, but decreases with aging beyond 50 years.

- Glomerular filtration rate declines with normal aging and mortality data supports the use of a lower range of glomerular filtration rate to define normal in the elderly compared to younger adults.

- There are substantial reasons to be concerned that a fixed glomerular filtration rate threshold of < 60 ml/min/1.73m² to define chronic kidney disease leads to over-diagnosis in the elderly and under-diagnosis in younger adults.
Sex and age-related GFR decline

<table>
<thead>
<tr>
<th>Age</th>
<th>Glomerular filtration rate, MDRD formula</th>
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</thead>
<tbody>
<tr>
<td>18–29</td>
<td>Male: 113.3, Female: 125.6, Total: 120.2</td>
</tr>
<tr>
<td>30–39</td>
<td>Male: 91.4, Female: 107.8, Total: 101.0</td>
</tr>
<tr>
<td>40–49</td>
<td>Male: 83.2, Female: 98.4, Total: 92.8</td>
</tr>
<tr>
<td>50–59</td>
<td>Male: 64.6, Female: 86.7, Total: 76.6</td>
</tr>
<tr>
<td>60–69</td>
<td>Male: 64.5, Female: 86.0, Total: 74.0</td>
</tr>
<tr>
<td>&gt;70</td>
<td>Male: 52.1, Female: 73.4, Total: 60.8</td>
</tr>
</tbody>
</table>
Renal functional reserve starts to decline with the loss of nephron number.

Two people may have the same GFR, but one might be more susceptible to acute kidney injury (AKI) and CKD progression than the other due to differences in renal reserve. The RFR acts as a sensitive method for the detection of subclinical kidney damage, and thus may help identify patients susceptible to kidney injury since it provides more information about whole kidney function and the remaining reserve.

Renal stress testing is useful in predicting the risk of developing kidney injury since it uncovers loss of renal functional mass when there is no clinical evidence of kidney injury.
Renal functional reserve is defined as the capacity of the kidney to compensate or increase its function in states of demand (e.g., high protein or fluid intake, pregnancy) or disease (e.g., diabetes, CKD).

In early diabetes, when nephron mass is still >50%, renal functional reserve may be reduced due to prevailing metabolic and (neuro)hormonal factors that increase baseline GFR. In later stages, additional renal hemodynamic adaptations occur in response to reduced renal mass, leading to continuous maximal use of glomerular filtration capacity.
Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease

Lowell J. Lo¹, Alan S. Go¹,²,³, Glenn M. Chertow⁴, Charles E. McCulloch⁵, Dongjie Fan², Juan D. Ordoñez⁵ and Chi-yuan Hsu¹,²

**AKI: progression toward CKD**

**Natural History of AKI**
Maladaptive repair following AKI
In case of a clinically evident AKI, a reduction in baseline GFR will become evident. In both cases, even if GFR returns to normal, recovery of renal function may be complete or partial. Complete or partial recovery will be documented by the assessment of RFR by a stress test.

In case of partial recovery and reduced RFR, the kidney may result more susceptible to further insults and develop clinically evident AKI even in the presence of a mild exposure.

A progressive defective repair will then progress towards CKD.
In patients with normal resting GFRs undergoing an elective cardiac operation, preoperative RFR was highly predictive of postoperative AKI. A reduced RFR appears to be a novel risk factor for AKI, and measurement of RFR may allow for preoperative identification of patients who are likely to benefit from preventive measures or biomarker monitoring to identify early AKI.

Larger prospective studies to validate the use of RFR alone or in combination with biochemical biomarkers are warranted.
Rate of acute kidney injury (AKI) and dialysis-requiring AKI (AKI-D; per 100 patient-years) in patients with different levels of transplant function (estimated glomerular filtration rate at 6 months after transplant in mL/min/1.73 m²)
Graft survival - DGF

<table>
<thead>
<tr>
<th>STRATA</th>
<th>No DGF</th>
<th>DGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>99.1</td>
<td>88.4</td>
</tr>
<tr>
<td>5 years</td>
<td>94.5</td>
<td>76.9</td>
</tr>
<tr>
<td>10 years</td>
<td>86.3</td>
<td>62.4</td>
</tr>
</tbody>
</table>

HR = 3.9 *
Delayed graft function in kidney transplantation

Norberto Perico, Dario Cattaneo, Mohamed H Sayegh, Giuseppe Remuzzi

Panel 1: Risk factors for delayed graft function

Procurement
- Kidneys from non-heart-beating donor
- Inotropic support of the donor
- Cold storage preservation
- Cold ischaemia time

Donor
- Age (>55 years)
- Marginal kidneys from diabetic or hypertensive donors

Recipient
Prerenal
- Recipient hypovolaemia
- Intraoperative albumin administration
- Nocturnal haemodialysis
- Haemodialysis with ultrafiltration within 24 h before Tx
- Recipient or donor bodyweight
- Number of previous transplants

Renal
- Inherited thrombophilia
- Factor V Leiden mutation
- OKT3 monoclonal antibody therapy
- Antiphospholipid antibodies
- Preformed antidonor antibodies
- Acute tubular necrosis
- Ciclosporin nephrotoxicity

Postrenal
- Ureteral leakage
- Ureteral obstruction

Older dialysis patients

Older donors

Portrait of Victor Choquet
Paul Cèzanne

Renal Transplantation in Patients Over 65 Years of Age: No More a Contraindication but a Growing Indication


‘Old-for-old’—new strategies for renal transplantation

Wolfgang Arns1, Franco Citerio2 and Josep M. Campistol3
The question......

RFR in Living Donor KTx?
OUTLINE

• Definition and evaluation of Renal Functional Reserve (RFR);

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Living Donor Kidneys Last Longer
Well matched living donor kidneys last even longer

Ten Year Overall Adjusted Graft Survival
Pre-emptive Living Donor Transplant vs. Dialysis

Graft half life. The point in time when exactly 50% of kidneys are still functioning.

Deceased Donor Kidney Transplant

Living Donor Kidney Transplant

Pre-Emptive Transplant

After 24 Months on Dialysis

*Source: 2010 OPTN/SRTR Annual Data Report, Published in American Journal of Transplantation 2012 12 (Suppl1)

*Source: Meier-Kriesch HU, Kaplan B., Transplantation, 2002 Nov 27; 74 (10): 1377-81
The problem of “medically complex” Kidney Donors

**DONOR AGE**

- **Obesity**
  - 1998-2001
  - 2002-2006
  - 2007-2010

- **Hypertension**
  - 1998-2001
  - 2002-2006
  - 2007-2010

- **Hypothyroidism**

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**Età dei donatori**

- 0
- 10
- 20
- 30
- 40
- 50
- 60

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9

**% donatori**

- 18-34
- 35-49
- 50-64
- 65+

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*37th Vicenza Course on AKI & CRRT – May 28-30, 2019*
The risks of Kidney Donors……..
The risks of Kidney Donors…….
After nephrectomy, as a result of the decrease of the nephron mass, kidney donors (KD) develop a partial loss of renal function, defined as AKI (Acute Kidney Injury) according to KDIGO criteria (2012).

The improvement in renal function is due to the Renal Functional Reserve (RFR).

Living donor kidney transplant can be performed thanks to RFR which ensures good renal function to both – the recipient and the donor (after the donation).
Kidney donor evaluation
Novara-UPO Kidney Tx Center

Serum creatinine with eGFR (CKD-EPI)
Complete urinalysis
Creatinine clearance
24-hour urine protein (including albuminuria)
Tubular function tests (if necessary)
Abdominal angio CT scan with CM and 3D reconstruction of kidney vessels and urinary tract
Sequential functional scintigraphy + Radioisotopic GFR
Kidney stress test with protein load (IRRIV – Vicenza protocol)
Radioisotopic GFR using $^{51}$Cr-EDTA, measures the overall renal function.

Sequential functional scintigraphy with $^{99mTc}$-MAG is necessary to determine split renal function (cortical phase).

Table of Result Summary:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Left</th>
<th>Right</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Split Function (%)</td>
<td>51.4</td>
<td>48.6</td>
<td></td>
</tr>
<tr>
<td>Kidney Counts (cpm)</td>
<td>25016</td>
<td>23652</td>
<td>48669</td>
</tr>
<tr>
<td>Time of Max (min)</td>
<td>4.668</td>
<td>5.668</td>
<td></td>
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</table>

$rGFR$ left $= 51.4 \text{ mL/min}$

$rGFR$ right $= 48.6 \text{ mL/min}$

$rGFR$ total $= 100 \text{ mL/min}$
RFR evaluation: oral protein load

Hydration: 8 mL/kg weight

2 determinations of creatinine clearance pre-load (basal)

Protein oral load: 1.2 gr. of proteins/kg weight

3 determinations of creatinine clearance post-load (1.5, 2.5 and 3.5 hours after protein oral load)

RFR = CrCl max post-load – Average basal CrCl
Patients and Methods

48 KD renal functions were evaluated:
- before donation with serum creatinine, eGFR (CKD-EPI), radioisotopic GFR (51Cr-EDTA) and a concomitant scintigraphy using 99mTc-MAG to assess the split renal function
- in the immediate postoperative period with serum creatinine
- one year after nephrectomy using 51Cr-EDTA

The results were then compared with the split radioisotopic GFR (51Cr-EDTA) of the right kidney at the first scintigraphic evaluation.
## Kidney Donors enrolled in the study

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>Description</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>20 (36%)</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>55 (49-63; 30-76)</td>
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<tr>
<td>Height (cm)</td>
<td>165 (159-173; 147-190)</td>
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</tr>
<tr>
<td>Weight (Kg)</td>
<td>70 (60-82; 43-113)</td>
<td></td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25.8 (23.2-28.3; 17.9-32.3)</td>
<td></td>
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<tr>
<td>BSA (m²)</td>
<td>1.75 (1.64-1.94; 1.34-2.38)</td>
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</tr>
<tr>
<td>Hypertension</td>
<td>12 (24%)</td>
<td></td>
</tr>
<tr>
<td>Abnormal Lipid Levels</td>
<td>23 (42%)</td>
<td></td>
</tr>
<tr>
<td>Active Smoking</td>
<td>6 (11%)</td>
<td></td>
</tr>
<tr>
<td>Baseline sCr (mg/dL)</td>
<td>0.70 (0.6-0.84; 0.5-1.02)</td>
<td></td>
</tr>
<tr>
<td>Baseline eGFR (CKD-EPI) (mL/min/1.73m²)</td>
<td>101 (93-105; 69-119)</td>
<td></td>
</tr>
<tr>
<td>Baseline CrCl (mL/min/1.73m²)</td>
<td>111 (90.25-139.75; 67.4-171.1)</td>
<td></td>
</tr>
<tr>
<td>Baseline mGFR (51Cr-EDTA)</td>
<td>98 (89-108; 77.4-129)</td>
<td></td>
</tr>
<tr>
<td>Functional Contribution Right Kidney (%)</td>
<td>47.4 (46-49.7; 43-56)</td>
<td></td>
</tr>
<tr>
<td>mGFR Right Kidney pre-donation (mL/min)</td>
<td>46.6 (42-53.4; 38.4-65)</td>
<td></td>
</tr>
</tbody>
</table>
Renal function post-nephrectomy

Zenit sCr: 1.22 mg/dL (range 1.11-1.44)

Average % of sCr increase: 79% (50-112%) in the first 48 hrs post-surgery.

All «AKI» Stage 1 (KDIGO 2012)
Renal function post-nephrectomy-2

7th POD sCr: 1.04 mg/dL (range 0.92-1.28)

Evaluation of sCr at 7th POD: gain of renal function of about 30% in comparison to Zenit.
BIOMARKERS OF TUBULAR INJURY

- NGAL

[TIMP-2]·[IGFBP7] (NephroCheck®)

RFR test before kidney donation:
- NGAL negative
- [TIMP-2]·[IGFBP7] negative

VII POD:
- NGAL negative
- [TIMP-2]·[IGFBP7] negative

1 year:
- NGAL negative
- [TIMP-2]·[IGFBP7] negative

Glomerular stress does not cause Tubular injury!!!!!

Is it true AKI?

No progression from AKI to CKD!!!!!
mGFR of the right kidney before donation

Radiosotopic GFR (51Cr-EDTA) of the right kidney: 46.6 mL/min
(42-53.4; 38.4-65)
mGFR of the remainant right kidney 1 year after left nephrectomy

Radiosotopic GFR (51Cr-EDTA) of the right kidney: 64 mL/min (58-71; 44-87)

Compensatory increase of GFR:
18.2 mL/min (10.3-22.6; 0.8-45.6), 34.5% (20-48.4; 1.4-110)
CORRELATION BETWEEN RFR BEFORE NEPHRECTOMY AND PERCENTAGE INCREASE OF GFR 1 YEAR AFTER DONATION

Linear correlation between pre-donation RFR and compensatory GFR increase 1 year after surgery ($r=0.6$)
RFR 1 year post-nephrectomy

RFR PRE-DONATION: 21.7 mL/min/1.73m² (0.09-51.96)

RFR POST-DONATION: 16.5 mL/min/1.73m² (2.66-21.97)
CONCLUSIONS

• Renal Functional Reserve (RFR) is an easy and feasible glomerular stress test.

• RFR is useful to better define kidney function in both physiological and pathologic conditions (pregnancy, aging kidney, hyperfiltration states including diabetes, CKD, etc.).

• RFR allows the identification of patients at high risk of developing AKI and progression from AKI to CKD in both native and transplanted kidneys.

• RFR is a good indicator of the compensatory increase of GFR after nephrectomy for LDKTx.
Thank you for the attention

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