Single nephron GFR

Actualités néphrologiques Jean Hamburger

23 Avril 2018

Marie Courbebaisse,
Service de Physiologie
Hôpital Européen Georges Pompidou, Paris

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Inserm

FACULTÉ DE MÉDECINE PARIS DESCARTES

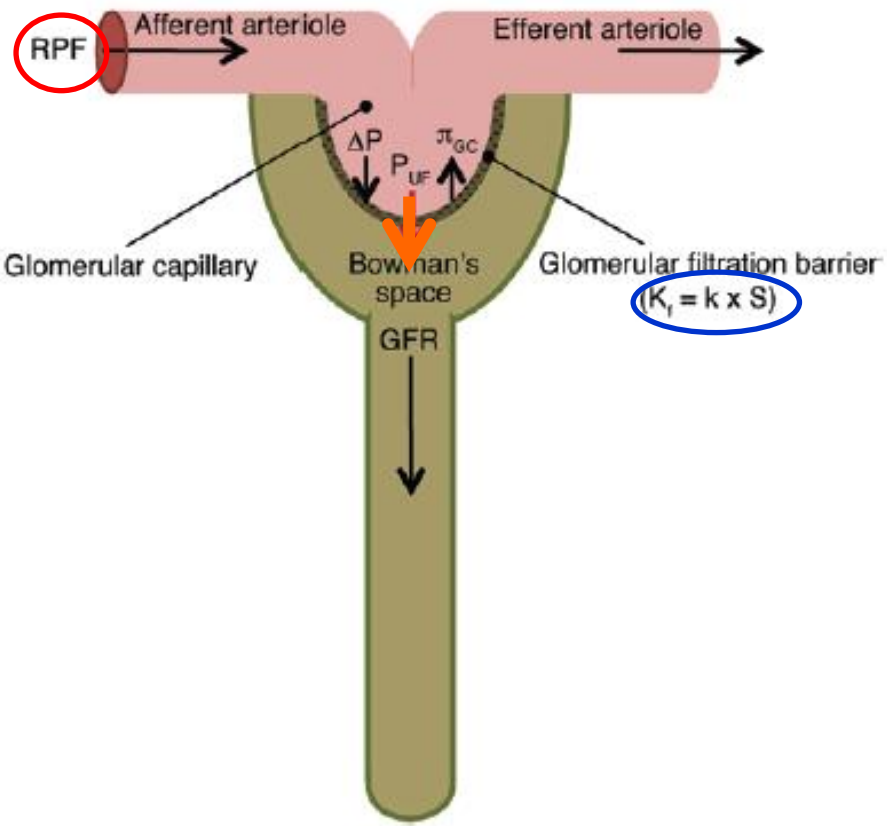
Introdution

- Glomerular filtration and SNGFR
- SNGFR in Healthy Adults
- Effect of nephronic reduction on SNGFR

Introdution

- Glomerular filtration and SNGFR
- SNGFR in Healthy Adults
- Effect of nephronic reduction on SNGFR

Glomerular Filtration



At a given RPF (renal plasma flow)

$$GFR = K_f x P_{uf}$$

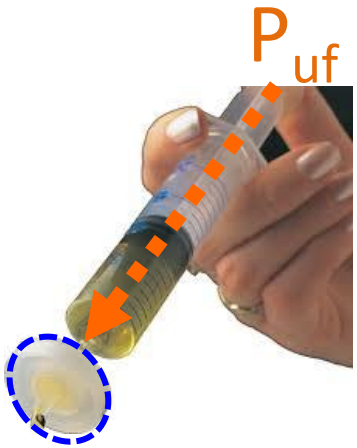
Ultrafiltration coefficient

Ultrafiltration pressure

Lenihan CR J Clin Invest, 2015

Glomerular Filtration

$$GFR = K_F x P_{UF}$$



K_F = Ultrafiltration coefficient

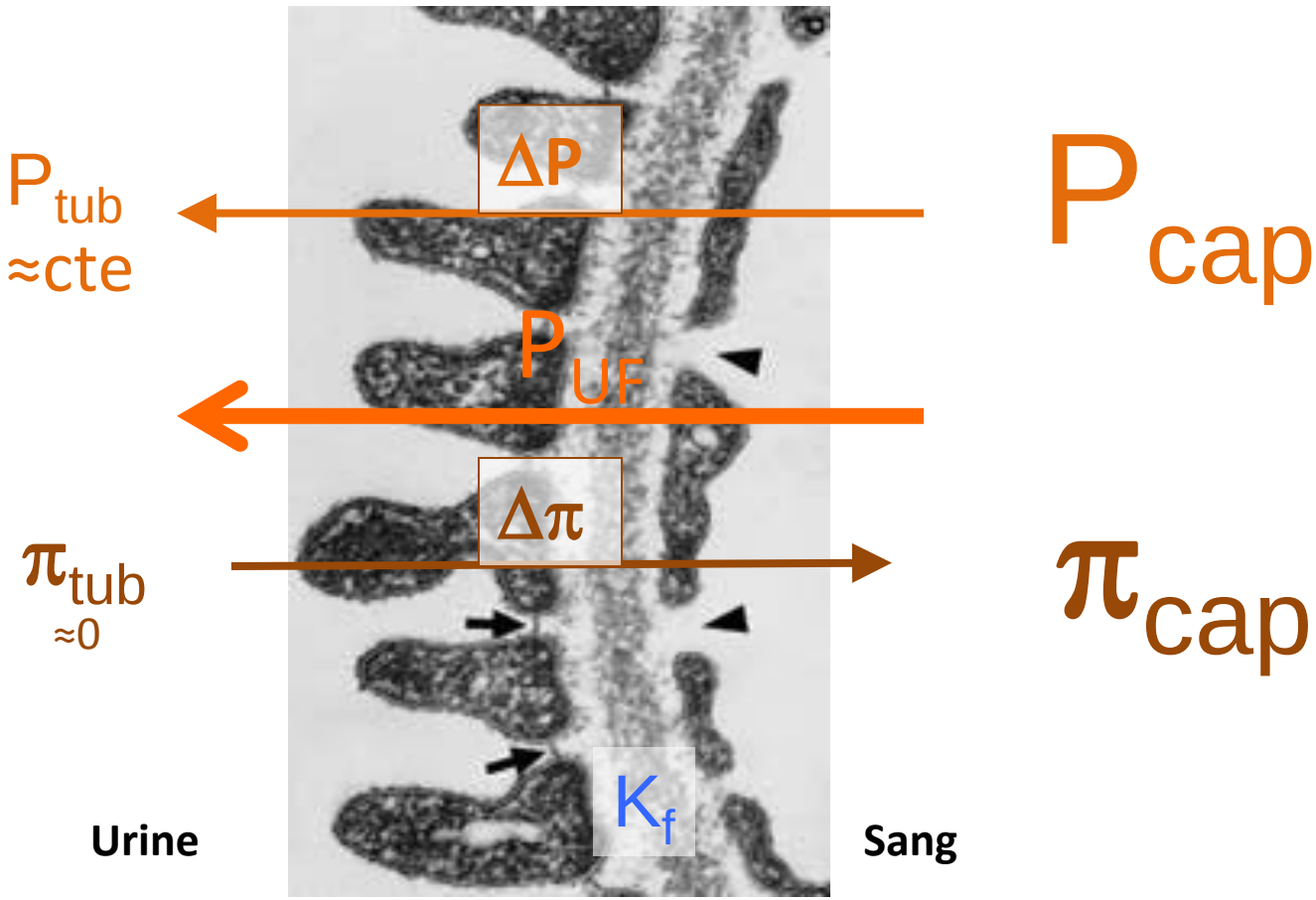
= hydraulic permeability*surface area=k*S

Glomerular filtration

$$GFR = K_F x P_{UF}$$

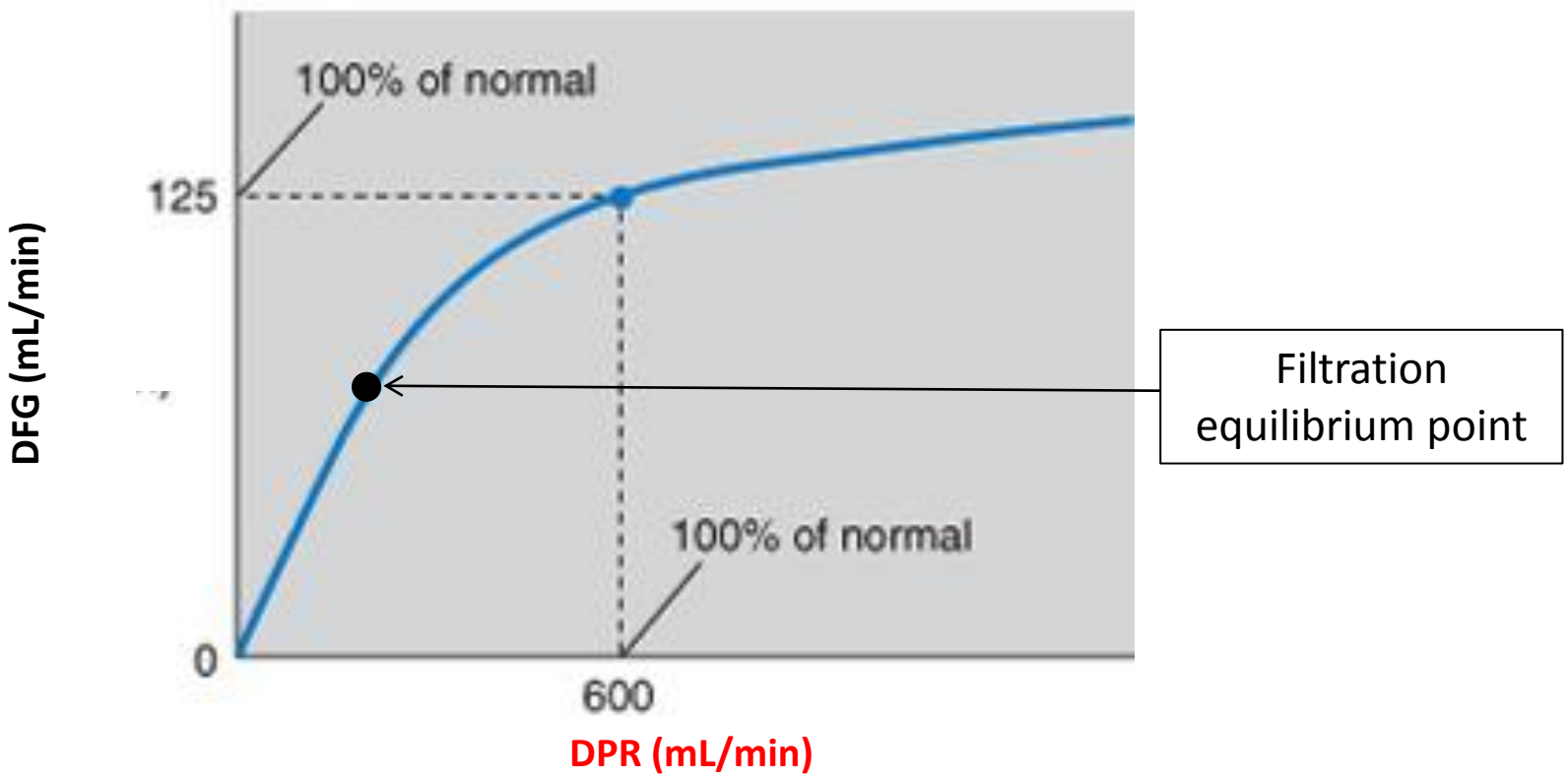
Determined by Starling's forces across the glomerular capillary

$$P_{UF} = \underbrace{[P_{cap} - P_{tub}]}_{\Delta P} - \underbrace{[\pi_{cap} - \pi_{tub}]}_{\Delta \pi} = \Delta P - \pi_{cap}$$



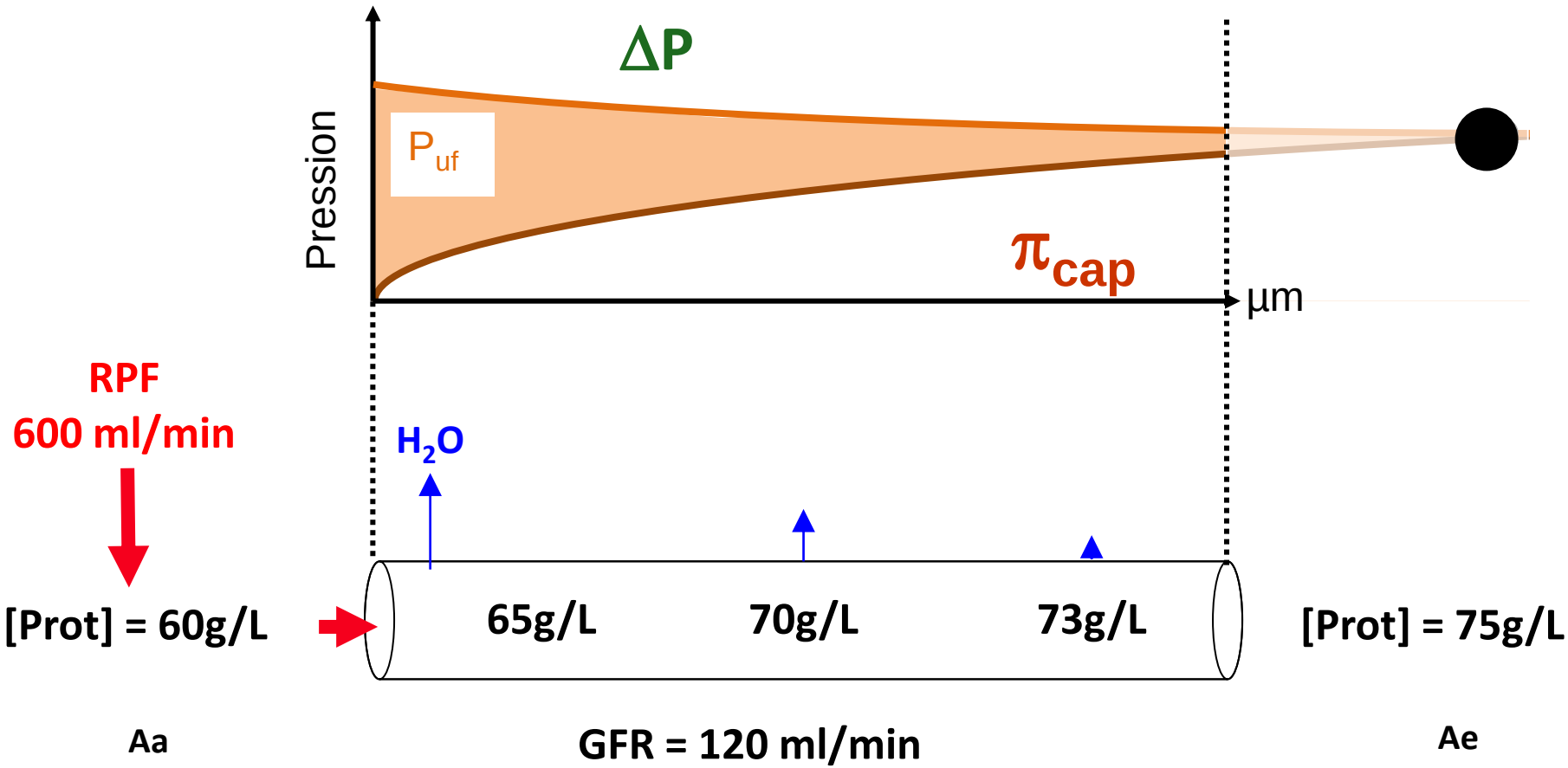
Glomerular Filtration

Relation between GFR and RPF



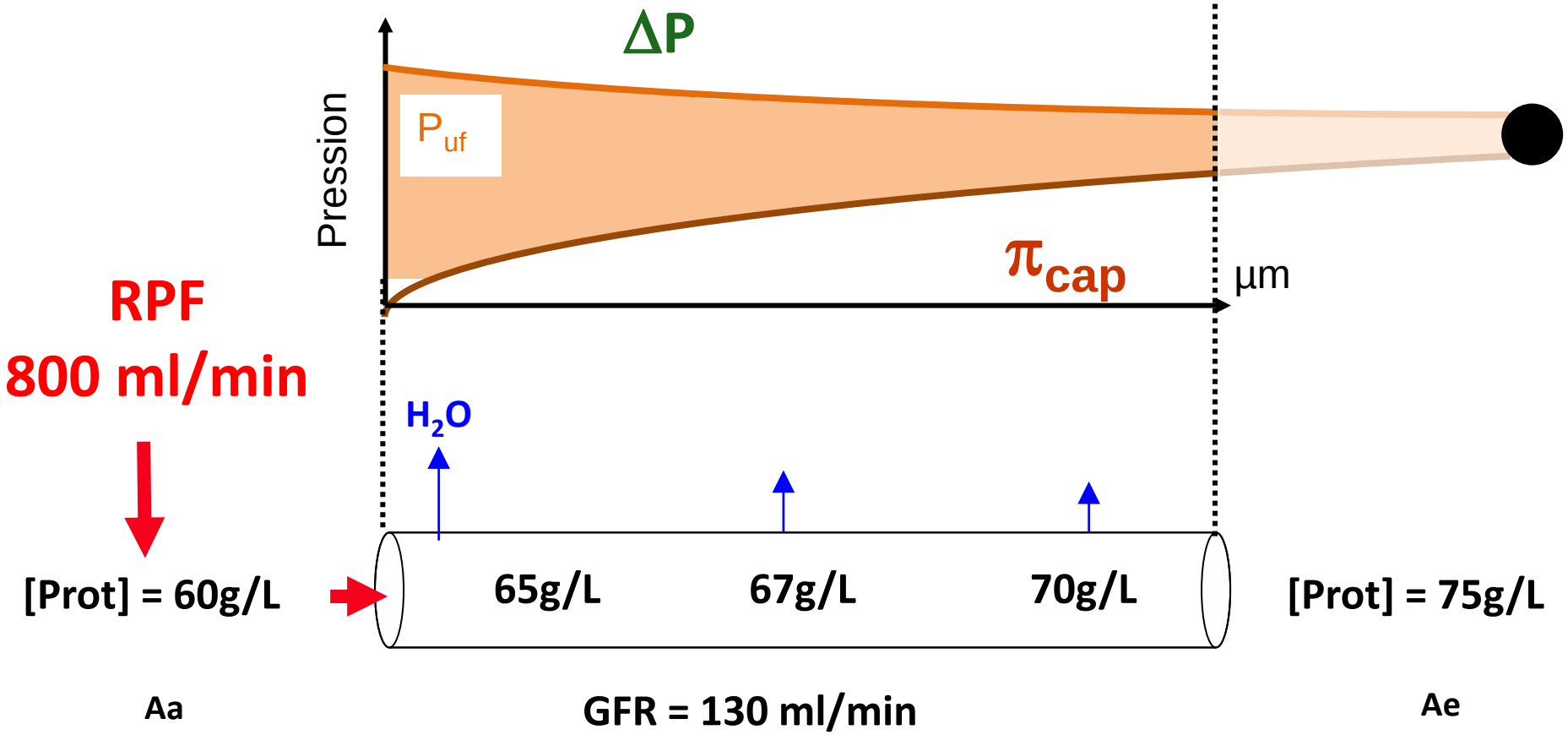
π_{cap} increases along the glomerular capillary

$$P_{uf} = \Delta P - \pi_{cap}$$



The increase in RPF diminishes the rate of increase in π_{cap} along the glomerular capillary, thereby increasing the PUF and GFR

$$P_{uf} = \Delta P - \pi_{cap}$$



Single nephron GFR

$GFR = K_F * P_{UF} = (k*S)*(\Delta P - \pi_{cap})$

GFR = Σ**SNGFR** **=** number of functional nephrons*__SNGFR__

GFR = number of functional nephrons* $[K_F * P_{UF}]$**SN**

GFR = number of functional nephrons* $[(k*S)*(\Delta P - \pi_{cap})]$**SN**

Single nephron GFR

GFR = number of functional nephrons*SNGFR

$$GFR = \text{number of functional nephrons} * [\underbrace{(k*S)}_{K_F} * \underbrace{(\Delta P - \pi_{cap})}_{P_{UF}}]SN$$

- Determined by birth weight *(Brenner BM, Am J Kidney Dis, 1994)*
- Can only decrease (aging *(Denic A, J Am Soc Nephrol, 2017)*, hypertension *(Lenihan CR, J Am Soc Nephrol, 2015)*, CKD, nephrectomy)

To limit – or to prevent - the reduction of GFR in the event of a decrease in the number of functional nephrons → **Increase in SNGFR**

- Increase in K_F → Increasing the surface of the filtration membrane (reflected by the increase in nephron size)
- Increase in P_{UF} → Increase in ΔP →Increase in Pcap
  → Decrease in π_{cap} →Increase in RPF

Single nephron GFR

"Among the various hemodynamic changes that occur within residual nephrons, the increase in glomerular pressure is the most important in generating subsequent pathologic changes."
Remnant kidney sydrome

Hostetter TH, Semin Nephrol, 2003: Hyperfiltration and glomerulosclerosis.

To limit – or to prevent - the reduction of GFR in the event of a decrease in the number of functional nephrons → **Increase in SNGFR**

- Increase in K_F → Increasing the surface of the filtration membrane (reflected by the increase in nephron size)

- Increase in P_{UF} → Increase in ΔP →Increase in Pcap

→ Decrease in π_{cap} →Increase in RPF

- Glomerular filtration and SNGFR
- SNGFR in Healthy Adults
- Effect of nephronic reduction on SNGFR

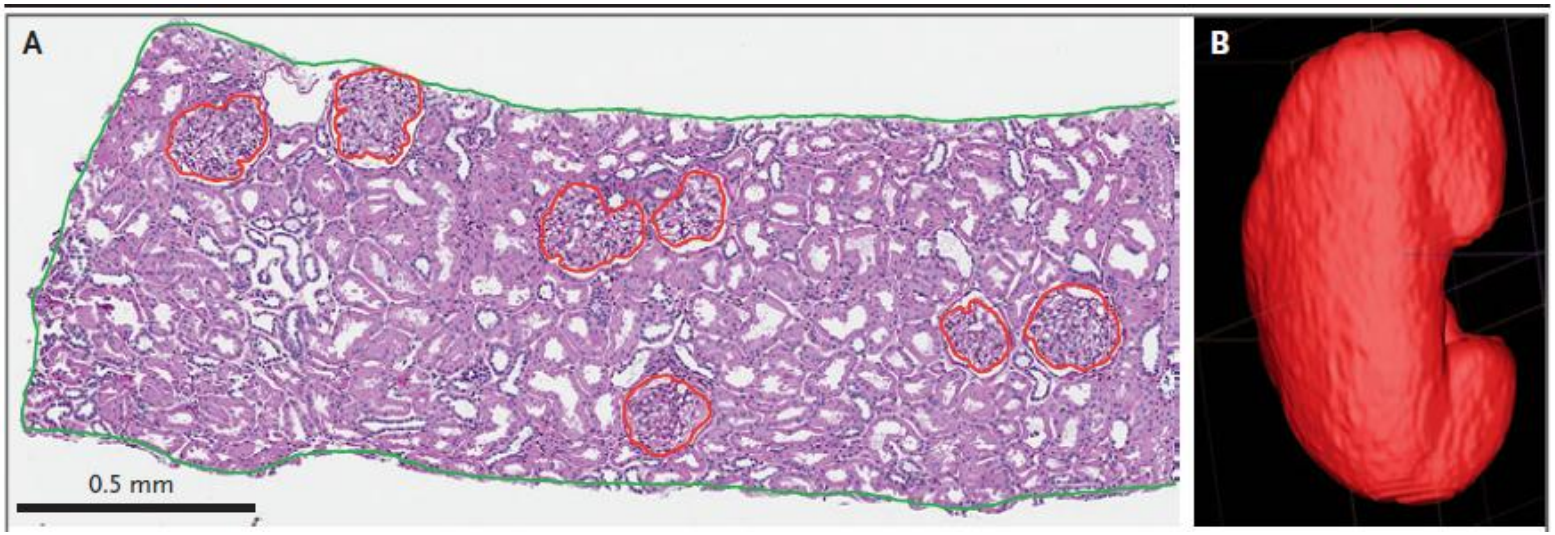
SNGFR in Healthy Adults

1388 living kidney donors at the time of donation (Minnesota and Ohio)

- CT-scan → Cortical volume
- Iothalamate clearance → Measurement of total GFR
- Needle core biopsy of the renal cortex during surgery (at least 2 mm^2 of cortex and 4 glomeruli)

→ Nephron size: mean nonsclerotic glomerular volume and mean cross-sectional tubular area
→ Glomerulosclerosis, interstitial fibrosis et arteriosclerosis

total number of nephrons = density of nonsclerotic glomeruli *cortical volume of both kidneys
SNGFR = total GFR/ total number of nephrons



Denic A, New Engl J Med, 2017

SNGFR in Healthy Adults

The number of nephrons per kidney and the total GFR both decline with age, whereas the SNGFR remains stable …at least until 70 years of age

Decrease in metabolic demand?

Table 2. Age-Group Differences in the Number of Nephrons per Kidney, the Single-Nephron GFR, and Total GFR among 1388 Living Kidney Donors.

Age Group	No. of Donors	No. of Nephrons	Single-Nephron GFR	Total GFR
			nl/min	*ml/min*
18–29 yr	190	970,000±430,000	79±42	127±25
30–39 yr	339	930,000±350,000	77±36	124±24
40–49 yr	417	850,000±360,000	81±42	114±23
50–59 yr	300	810,000±360,000	80±40	106±20
60–64 yr	73	750,000±310,000	79±36	101±18
65–69 yr	56	720,000±260,000	76±33	95±17
70–75 yr	13	480,000±170,000	110±44	96±25

79 nl/min

p<0,001

Denic A, New Engl J Med, 2017

SNGFR in Healthy Adults

Number of nephrons and total GFR lower in women than in men but …
SNGFR similar in men and women (81 nl per minute and 79 nl per minute, respectively; p=0.28)

Table 3. Demographic and Clinical Characteristics as Predictors of the Number of Nephrons per Kidney, Single-Nephron GFR, and Total GFR.*

Characteristic	No. of Nephrons		Single-Nephron GFR		Total GFR	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
			nl/min		*ml/min*	
Age, per 10 yr	–60,000	<0.001	1	0.28	–7.1	<0.001
Female sex	–60,000	0.03	6	0.08	–3.8	0.01
Body-mass index, per SD	0	0.85	6	<0.001	9.6	<0.001
Height, per SD†	30,000	0.03	4	0.006	9.2	<0.001
Uric acid, per SD	–40,000	0.002	1	0.42	–3.7	<0.001
Family history of end-stage renal disease	–70,000	<0.001	8	<0.001	0.8	0.43
Mild hypertension	–20,000	0.59	3	0.39	1.5	0.36

Denic A, New Engl J Med, 2017

SNGFR in Healthy Adults

Higher SNGFR independently associated with :

- higher BMI
- taller height (>190 cm)
- family history of end-stage renal disease

Table 3. Demographic and Clinical Characteristics as Predictors of the Number of Nephrons per Kidney, Single-Nephron GFR, and Total GFR.*

Characteristic	No. of Nephrons		Single-Nephron GFR		Total GFR	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
			nl/min		*ml/min*	
Age, per 10 yr	−60,000	<0.001	1	0.28	−7.1	<0.001
Female sex	−60,000	0.03	6	0.08	−3.8	0.01
Body-mass index, per SD	0	0.85	6	<0.001	9.6	<0.001
Height, per SD†	30,000	0.03	4	0.006	9.2	<0.001
Uric acid, per SD	−40,000	0.002	1	0.42	−3.7	<0.001
Family history of end-stage renal disease	−70,000	<0.001	8	<0.001	0.8	0.43
Mild hypertension	−20,000	0.59	3	0.39	1.5	0.36

Denic A, New Engl J Med, 2017

SNGFR in Healthy Adults

Higher SNGFR independently associated with:

- Nephrosclerosis (exceeding that expected for age)
  Glomerulosclerosis or arteriosclerosis
- Larger nephron size

Table 4. Biopsy-Sample Characteristics as Predictors of the Number of Nephrons per Kidney, Single-Nephron GFR, and Total GFR.*

Characteristic	No. of Nephrons		Single-Nephron GFR		Total GFR	
	Estimate	P Value	Estimate	P Value	Estimate	P Value
			nl/min		*ml/min*	
Nephrosclerosis						
Interstitial fibrosis	20,000	0.58	–8	0.11	–2.4	0.44
Glomerulosclerosis	–200,000	<0.001	22	<0.001	–1.1	0.58
Arteriosclerosis	–50,000	0.03	8	0.001	1.8	0.21
Nephron size						
Glomerular volume, per SD	–160,000	<0.001	18	<0.001	2.8	<0.001
Tubular area, per SD	–30,000	<0.001	4	<0.001	1.7	0.01

Denic A, New Engl J Med, 2017

SNGFR in Healthy Adults

The correlation between nephron size and SNGFR suggests that nephron size is an important determinant of SNGFR.

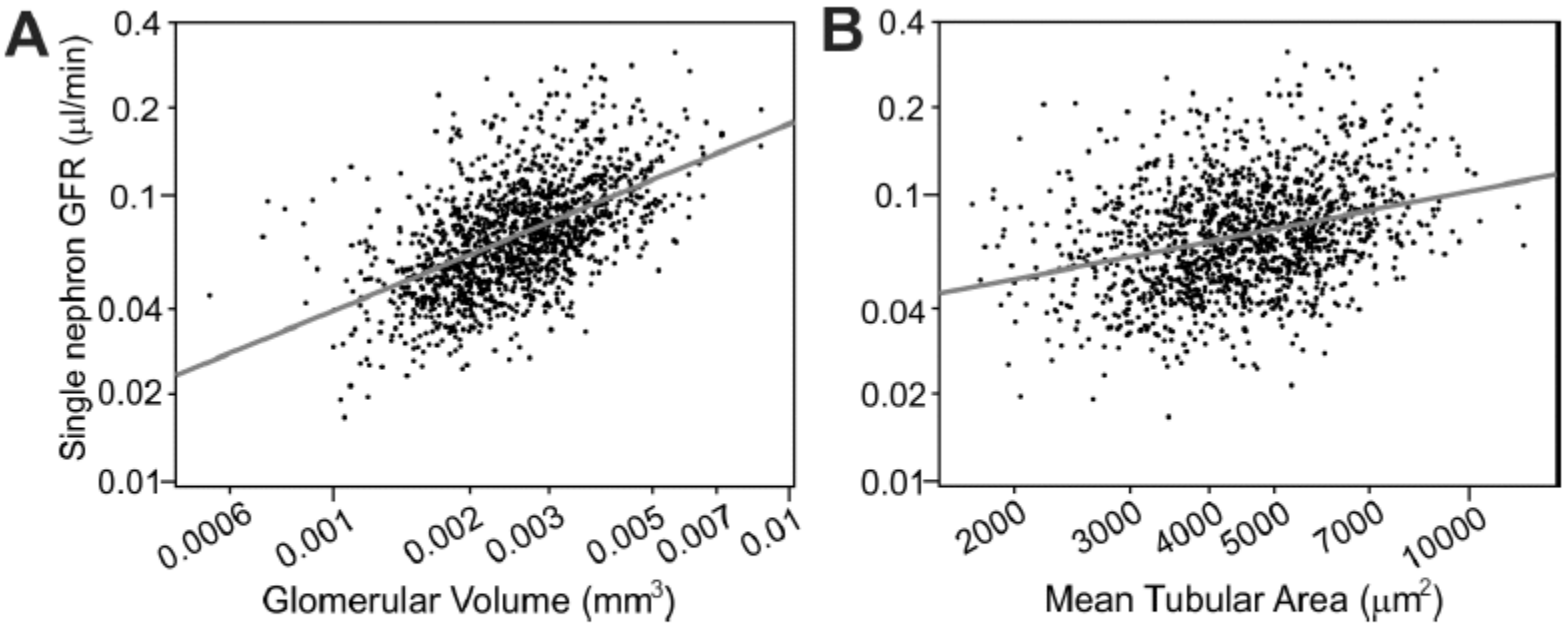


Figure S4. Nephron size correlates with single nephron glomerular filtration rate (snGFR).

Higher snGFR correlates with larger glomerular volume (r_s=0.55, p<0.0001) (**A**), and larger cross-sectional tubular area (r_s=0.32, p<0.0001) (**B**). The line is the regression fit on a log-log scale.

Denic A, New Engl J Med, 2017

SNGFR chez l'Homme en condition physiologique

The associations of a higher SNGFR with higher BMI, taller height, and family history of end-stage renal disease are attenuated after adjustment for nephron size
→increase in nephron size is the main reason to explain the increase in SNGFR.

Table S2. Clinical and biopsy characteristics as predictors of single nephron GFR (adjusted for each other characteristic in models that include different combinations of nephrosclerosis and nephron size; n=1210).

		Clinical only		Clinical and nephrosclerosis		Clinical and nephron size		Clinical and both biopsy findings	
	Characteristic	Estimate*	P Value	Estimate*	P Value	Estimate*	P Value	Estimate*	P Value
Clinical Characteristics	Age, per 10 years	1	0.30	-1	0.38	2	0.09	0	0.69
	Female	7	0.05	7	**0.03**	9	**0.003**	10	**0.001**
	BMI, per SD	7	**<0.001**	7	**<0.001**	2	**0.03**	3	**0.01**
	Height, per SD	4	**0.02**	4	**0.01**	2	0.20	2	0.13
	Uric acid, per SD	1	0.36	2	0.29	0	0.92	0	0.79
	Family history of end-stage renal disease	6	**0.006**	6	**0.01**	3	0.15	2	0.22
	Hypertension	1	0.76	1	0.82	-1	0.83	-1	0.74
Nephrosclerosis†	Glomerulosclerosis			22	**<0.001**			22	**<0.001**
	Arteriosclerosis			8	**0.003**			7	**0.002**
Nephron size	Glomerular volume, per SD					18	**<0.001**	17	**<0.001**
	Tubular area, per SD					4	**0.002**	4	**<0.001**

Denic A, New Engl J Med, 2017

SNGFR in Healthy Adults

- higher BMI
- taller height (>190 cm)
- family history of end-stage renal disease

$$\uparrow SNGFR = \uparrow K_{Fsn} * P_{UFsn}$$

$\uparrow K_{UF}$ = Hydraulic permeability* $\uparrow$Surface area

$\uparrow$Nephron size

- Glomerular filtration and SNGFR
- SNGFR in Healthy Adults
- Effect of nephronic reduction on SNGFR

Direct measurement of SNGFR

- In species with superficial glomeruli
- Inuline infusion
- **Micropuncture study**: tubular fluid collection

$$\text{SNGFR}_{\text{nl/min}} = \frac{U*V}{P} = \frac{[\text{Inuline}]\text{Tub}*\text{Tubule fluid flow rate}}{[\text{Inuline}]\text{P}}$$

Brenner BM, Am J Physiol 1972

Effect of nephronic reduction on SNGFR: Animal model

Nephronic reduction
(Right nephrectomy and infarction of approximately five-sixths of the left kidney)

↓

Increase in Glomerular plasma flow (concomittant decrease in Raa and Rae) and increase in ΔP

$$\uparrow SNGFR = \uparrow P_{UFsn} * \leftrightarrow K_{UFsn}$$

↓

Increase in SNGFR

Day 7

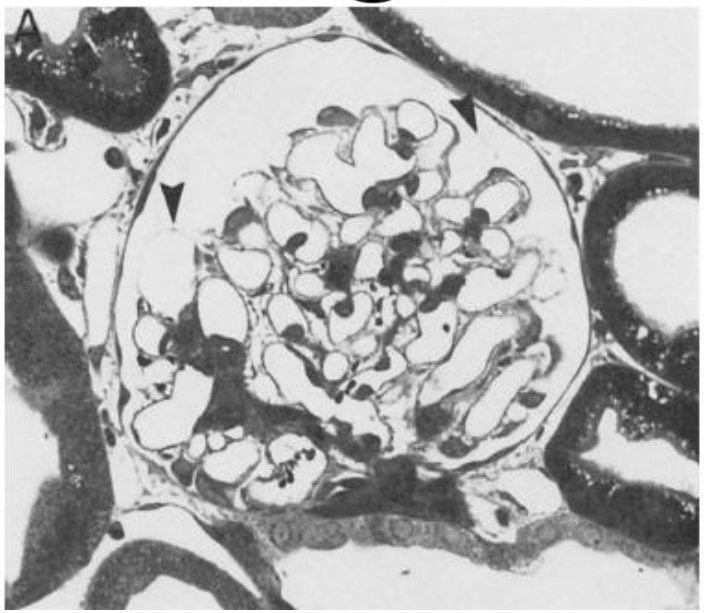


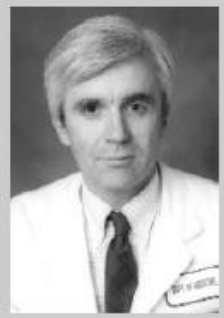
FIG. 1. Light micrographs of glomeruli from experimental rats 7 days following operation. *A: group II* rat. Note segmental increase in mesangium and blebs (arrowheads) in epithelial cells.
(Toluidine blue, ×300).

Hostetter TH, Am J Physiol, 1981

benign. We have not identified the factors that cause "compensatory" growth and increased perfusion of remnant glomeruli after reduction in nephron number, and we possess very imperfect knowledge of the extent to which interrupting these processes limits glomerular injury.

Hostetter TH, Am J Physiol, 1981

Hostetter TH, Brenner BM, Meyer TW, Millestone in Nephrology, J Am Soc Nephrol, 2001



AUTHOR COMMENTARY

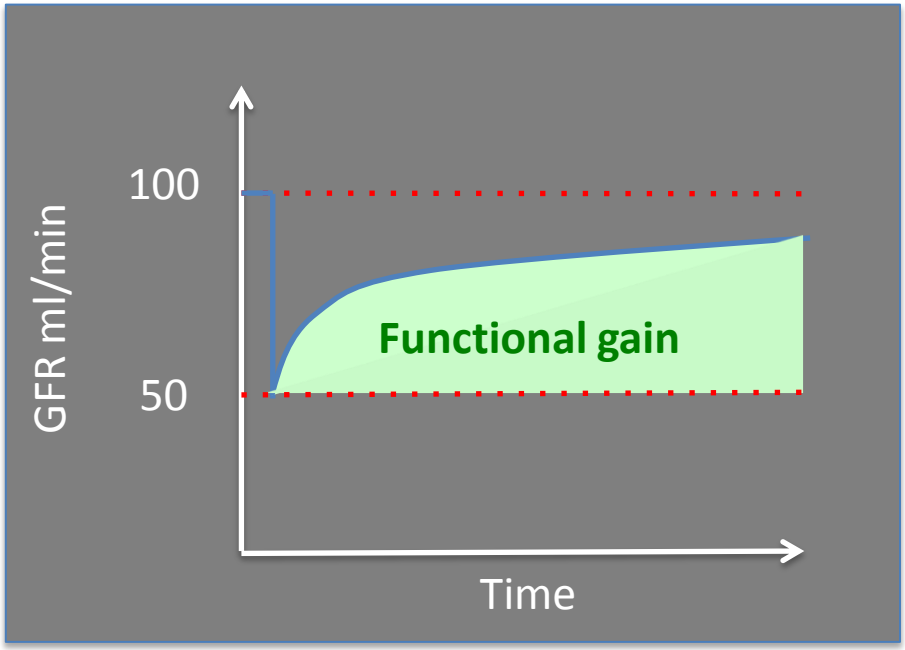
Thomas H. Hostetter

National Institute of Diabetes and Digestive and Kidney Diseases
National Institutes of Health
Bethesda, Maryland

Barry M. Brenner

Brigham and Women's Hospital and Harvard Medical School
Boston, Massachusetts

Effect of nephronic reduction on SNGFR: Human model → living kidney donors



After the donation, the number of nephrons of the remaining kidney can not increase.

As a result, the functional gain is exclusively due to an increase in the SNGFR.

Lenihan CR, J Clin Invest, 2015; Courbebaisse M, Clin J Am Soc Nephrol, 2016

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

- 21 living kidney donors
- immediately before, early after (median, 0.8 years), and late after (median, 6.1 years) living kidney donation.

Prior to transplantation: biopsy from the donated kidney
→ Filtration surface area (S) = filtration surface density *glomerular volume surface
→ Hydraulic permeability (k) = filtration slit frequency and thickness of the glomerular basement membrane (× 12,000)
→ K_F

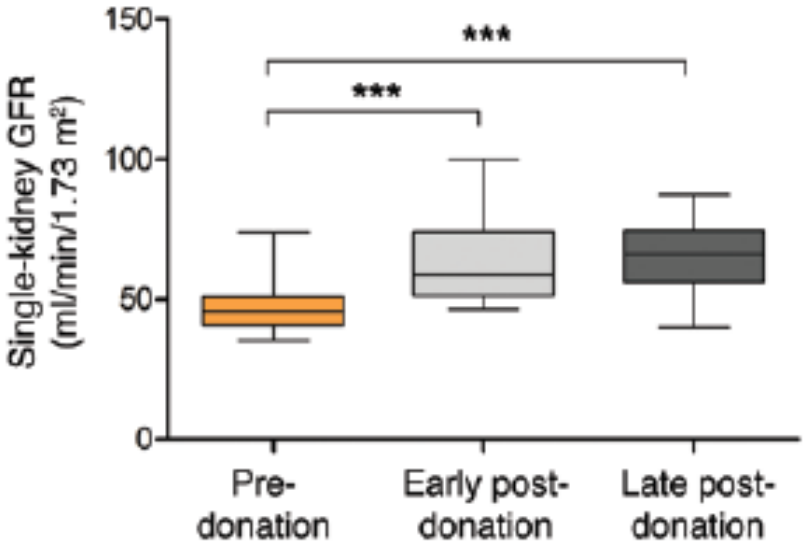
At each timepoint:
- Global GFR measurement (Iothalamate)
- RPF (PAH)
- Oncotic pressure (Serum albumin)
- Cortical volume (CT or MRI)

Estimation that the ΔP in healthy human glomeruli approximates 40 mmHg

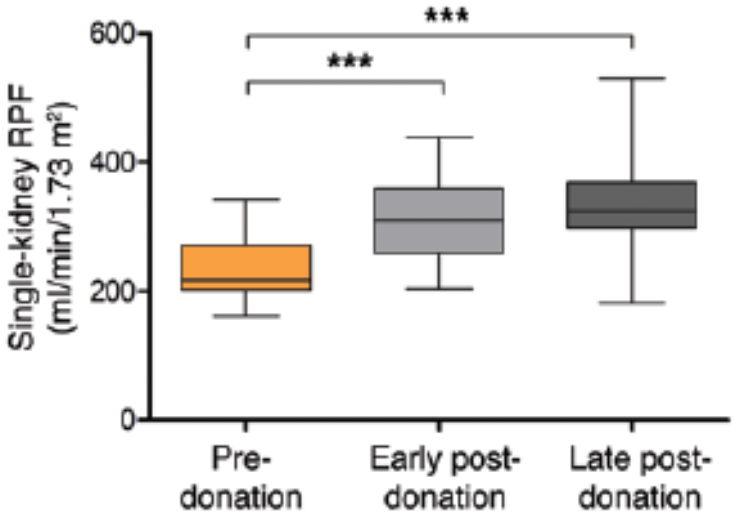
Lenihan CR, J Clin Invest, 2015

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

GFR of the remaining kidney



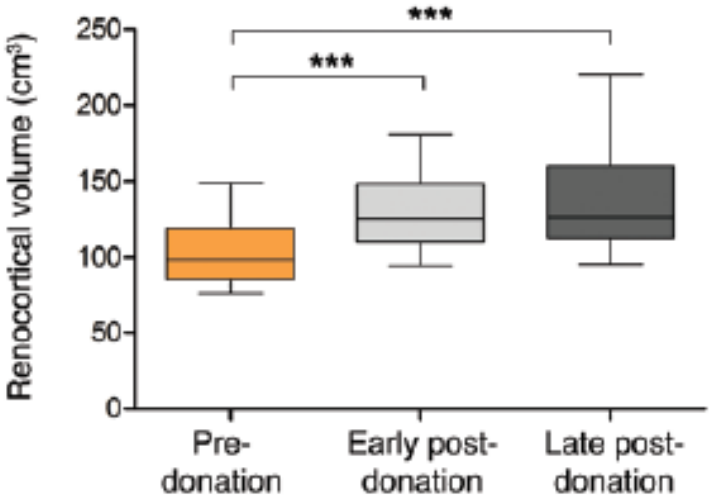
RPF of the remaining kidney



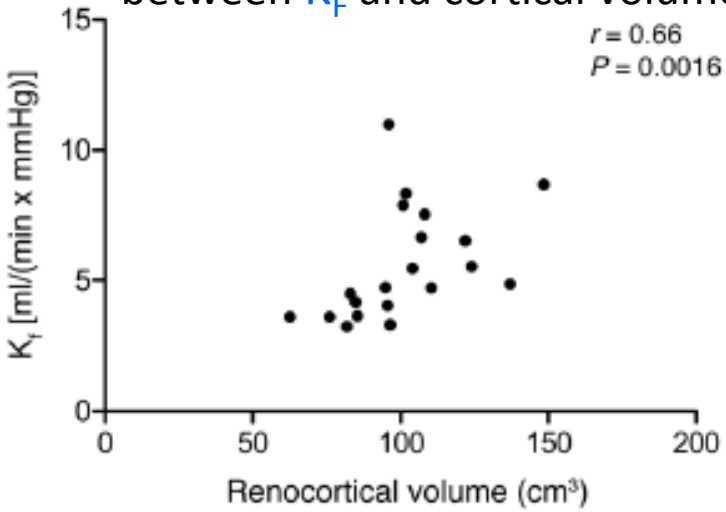
Lenihan CR, J Clin Invest, 2015

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

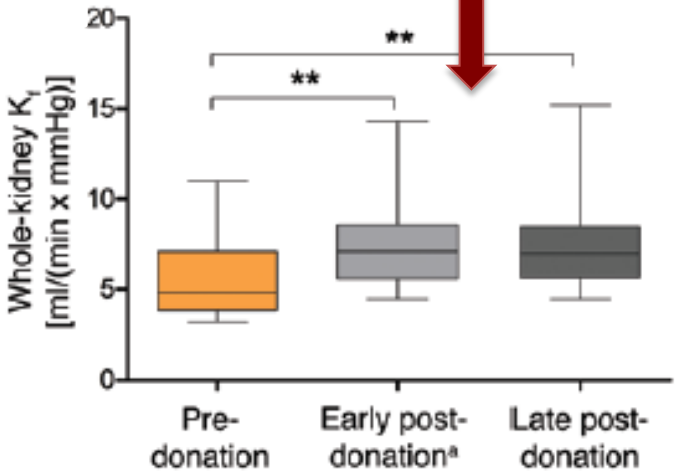
Volume of the remaining kidney



Before donation: Correlation between K_F and cortical volume



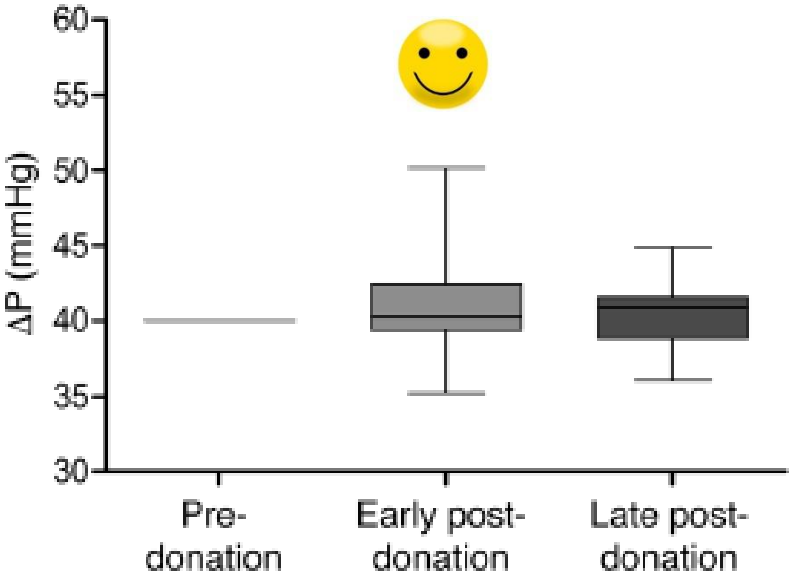
Assuming that glomerular hypertrophy and thus increased filtration area is proportional to the increase in cortical volume, the % of increase in cortical volume after donation was used to estimate the corresponding KF values.



Lenihan CR, J Clin Invest, 2015

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

This model was used to calculate the ΔP required to maintain the GFR measured after donation using these calculated K_F values.

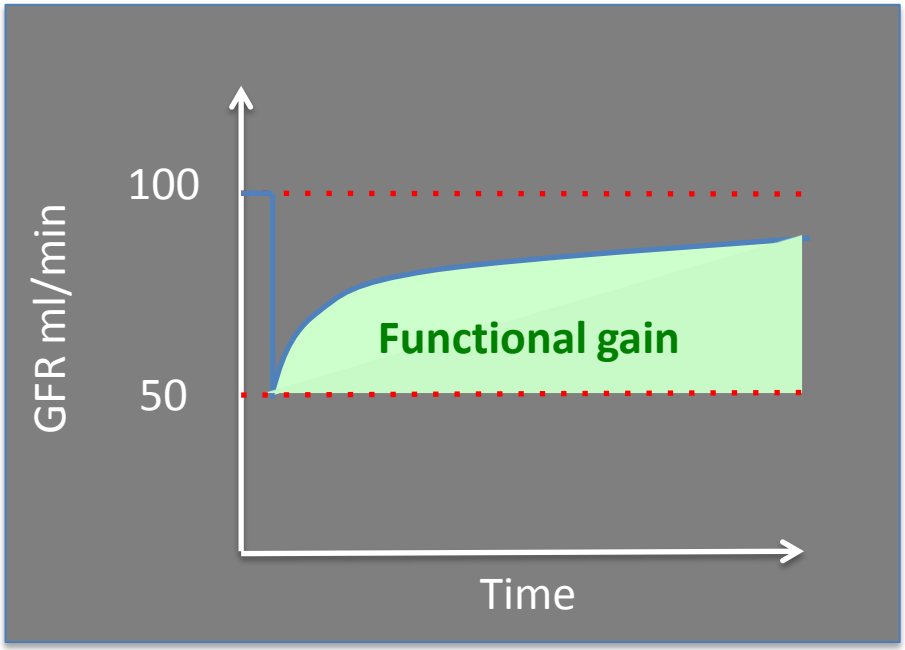


"Post-donation hyperfiltration by the remaining kidney is maintained stable by a combination of an increase in RPF and in the Kf resulting from compensatory glomerular hypertrophy.

Our modeling argues against the development of significant glomerular hypertension following donor nephrectomy".

Lenihan CR, J Clin Invest, 2015

Effect of nephronic reduction on SNGFR: Human model → living kidney donors



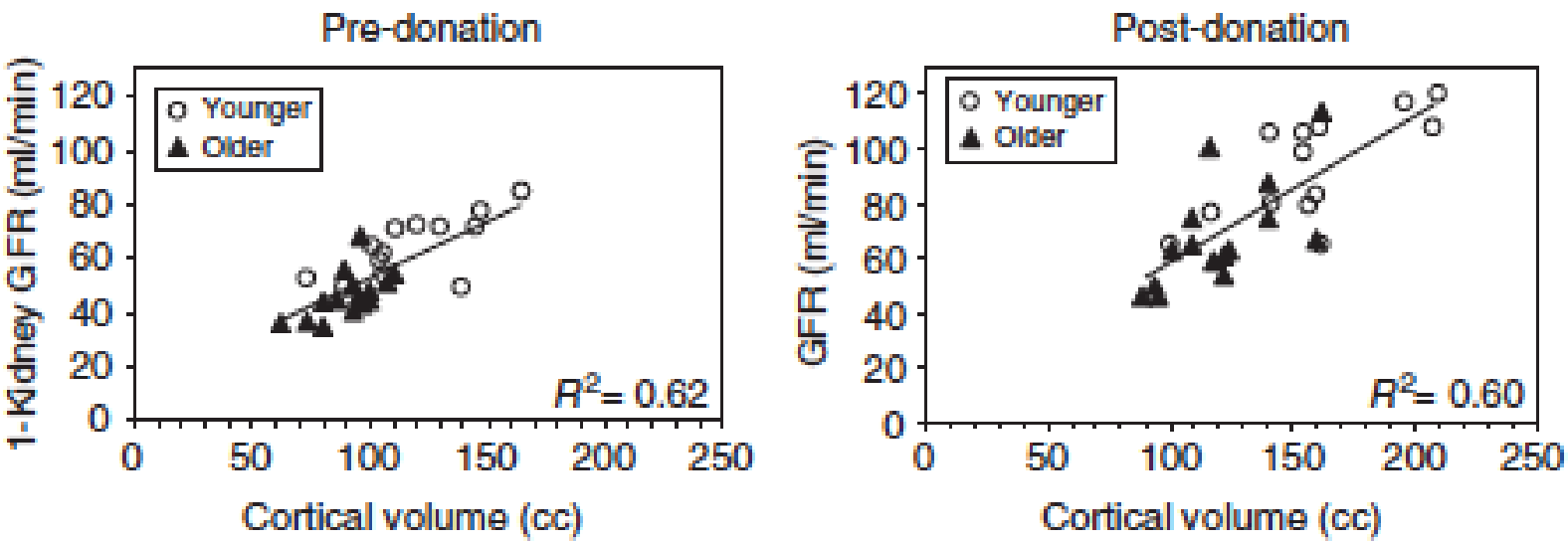
Initial GFR of the remaining kidney+ **Functional gain** = number of functional nephrons* ↑**SNGFR**

High SNGFR
- Age>70 yrs
- BMI
- Height (if ≥190 cm)
- Family history of end-stage renal disease
- Nephrosclerosis (exceeding that expected for age)

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

Aging?

33 LKD 45 ≤yrs versus 24 LKD ≥55-68 yrs



After donation, GFR and cortical volume increase in the same proportions in younger and older donors, suggesting a similar relative increase in SNGFR in both groups.

After 70 yrs?...

Tan JC, Kidney Int, 2010

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

Overweight?

The inverse association between BMI and functional gain after kidney donation has already been reported. *(Rook M, Am J Transplant, 2006; Courbebaisse M, CJASN, 2016)*

105 female donors <45 years
Renal functional reserve= rise in GFR (125I-Iothalamate clearance) during dopamine before and after kidney donation

Pre-donation GFR = 118 ml/min RFR = 10 ml/min

Post-donation GFR = 76 ml/min RFR = 4 ml/min

RFR = 1 ml/min in overweight donors

BMI inversely associated with RFR after donation

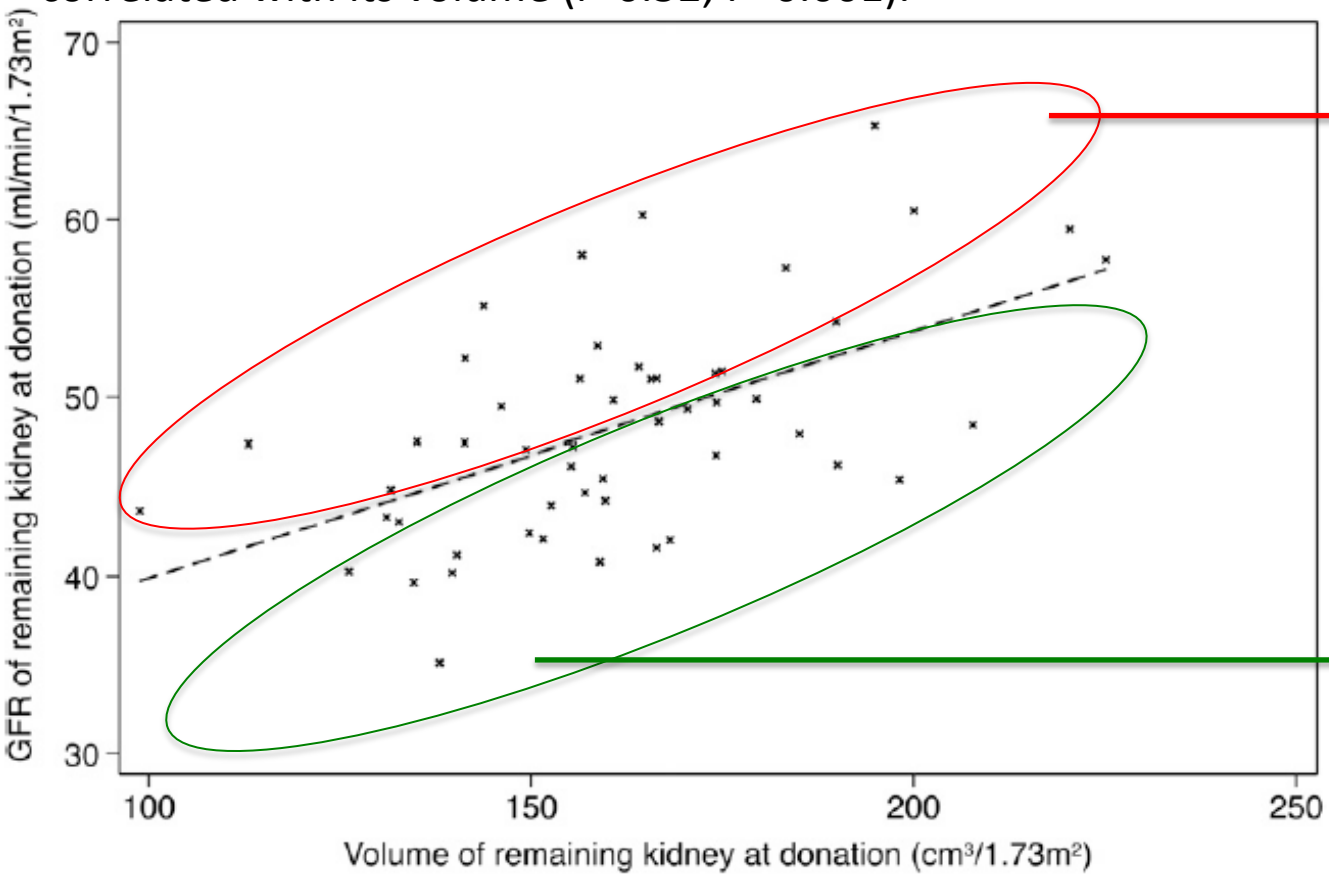
This result suggests that SNGFR can not increase further after donation in overweight donors.

Van Londen M, AJP Renal Physiol, 2018

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

GFR_{rk}/Vol_{rk}

Before donation, the GFR of the remaining kidney is positively correlated with its volume (r=0.52; P<0.001).



High GFR for a given Volume
High GFR/Vol

More « GFR » per unit of renal volume
→ One possible explanation:
higher SNGFR

Low GFR for a given volume
Low GFR/Vol
→Lower SNGFR

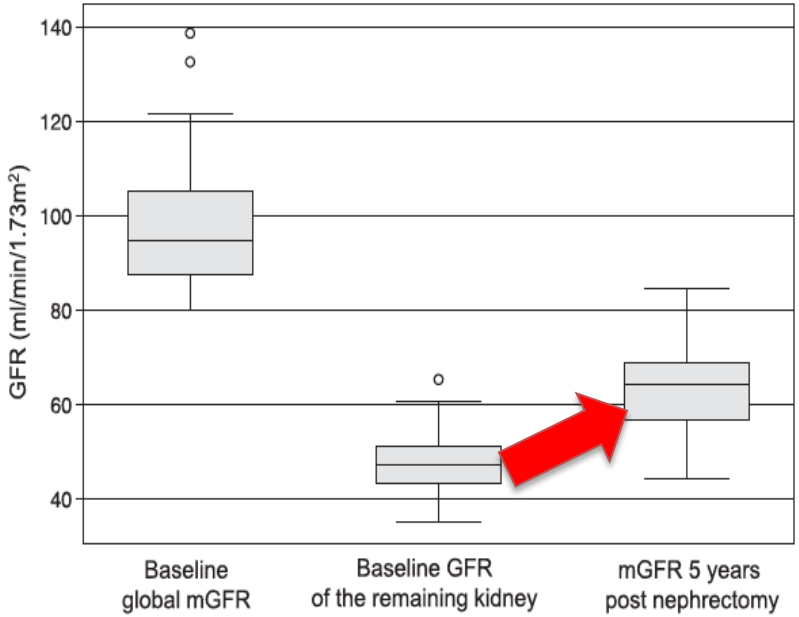
The new variable DFG/Vol of the remaining kidney, which may reflect SNGFR, should be inversely associated with the functional gain 5 years after donation

Courbebaisse M, CJASN, 2016

Effect of nephronic reduction on SNGFR: Human model → living kidney donors

GFR_{rk}/Vol_{rk}

63 LKD
GFR measurement before and 5 yrs after donation
SRF (Scintigraphy) before donation
Kidney volume (CT-scan) before donation (n=52)



	Development cohort			Validation cohort		
	coefficient	se	*p*	coefficient	se	*p*
Age at donation	-0.381	(0.070)	0.000	-0.115	(0.188)	0.543
BMI at donation	-0.337	(0.139)	0.019	-0.901	(0.443)	0.050
mGFR/vol	-55.094	-18.985	0.006	-97.557	-19.681	0.000
Observations		52			39	
R-squared		0.409			0.404	

Courbebaisse M, CJASN, 2016

Conclusion

- Despite substantial variation in the number of nephrons the SNGFR varied little according to Age (if <70 yrs), Sex and Height (if ≤190 cm) in healthy adults.

- SNGFR increases with BMI, Height ≥190 cm, Family history of end-stage renal disease and nephrosclerose.

- After kidney donation, the functional gain of the remaining kidney seems to be due to a combination of an increase in RPF and in the Kf resulting from compensatory glomerular hypertrophy.

- The new variable DFG/Vol of the remaining kidney, which may reflect SNGFR, is inversely associated with the functional gain after donation