Primärer Hyperaldosteronismus

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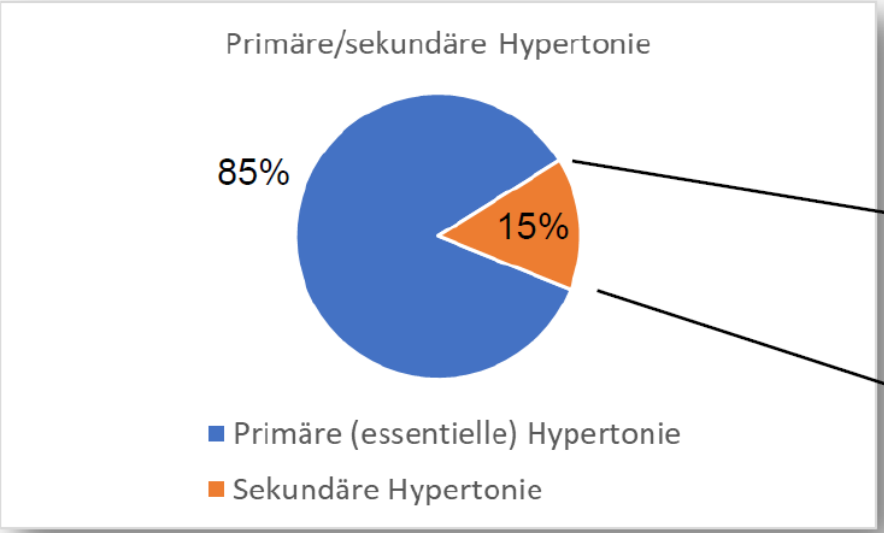
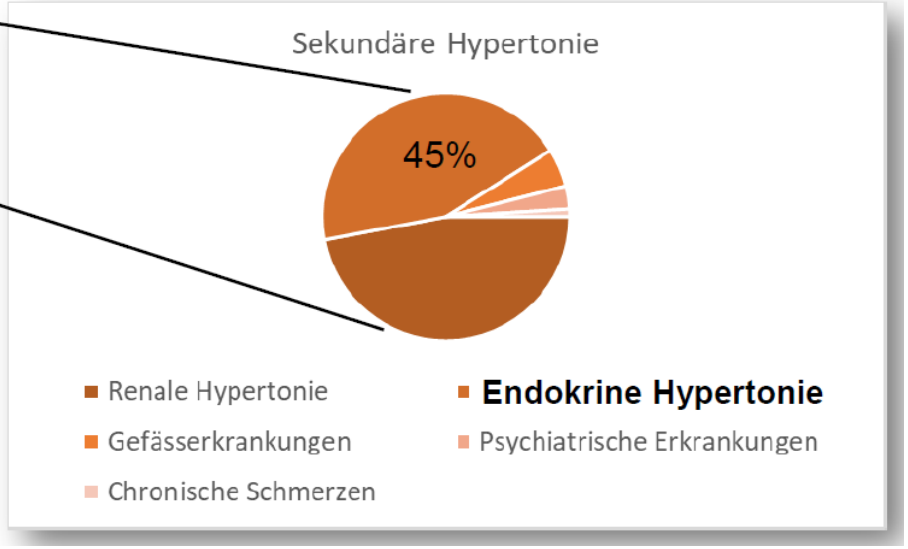
Arterielle Hypertonie

Hypertonie ist bei der Schweizer Bevölkerung im Alter von über 60 Jahren die **am häufigsten gestellte** medizinische Diagnose.

In mitteleuropäischen Ländern haben etwa 20% der Erwachsenen einen erhöhten Blutdruck





F. Beuschlein, 2018

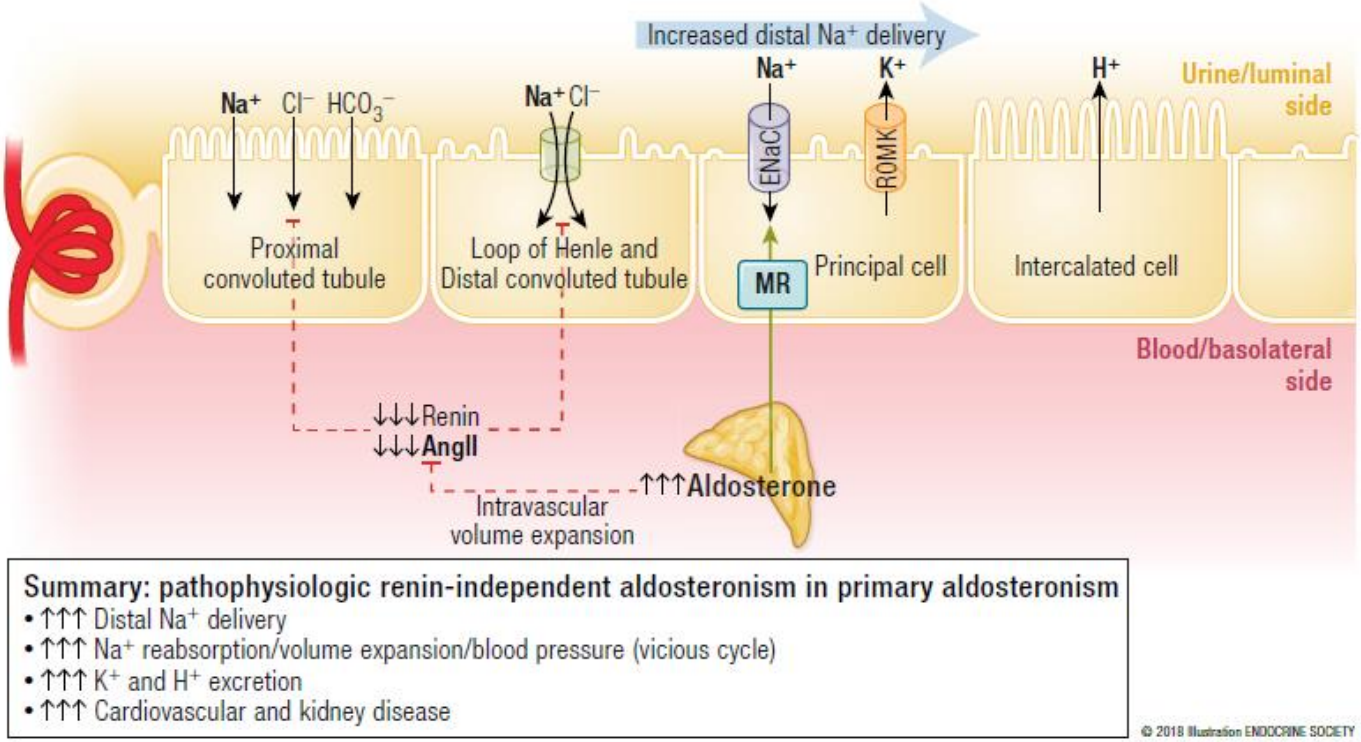
Endokrine Hypertonie

Cortisolexzess

Catecholamin-Exzess

Primärer Hyperaldosteronismus

Definition



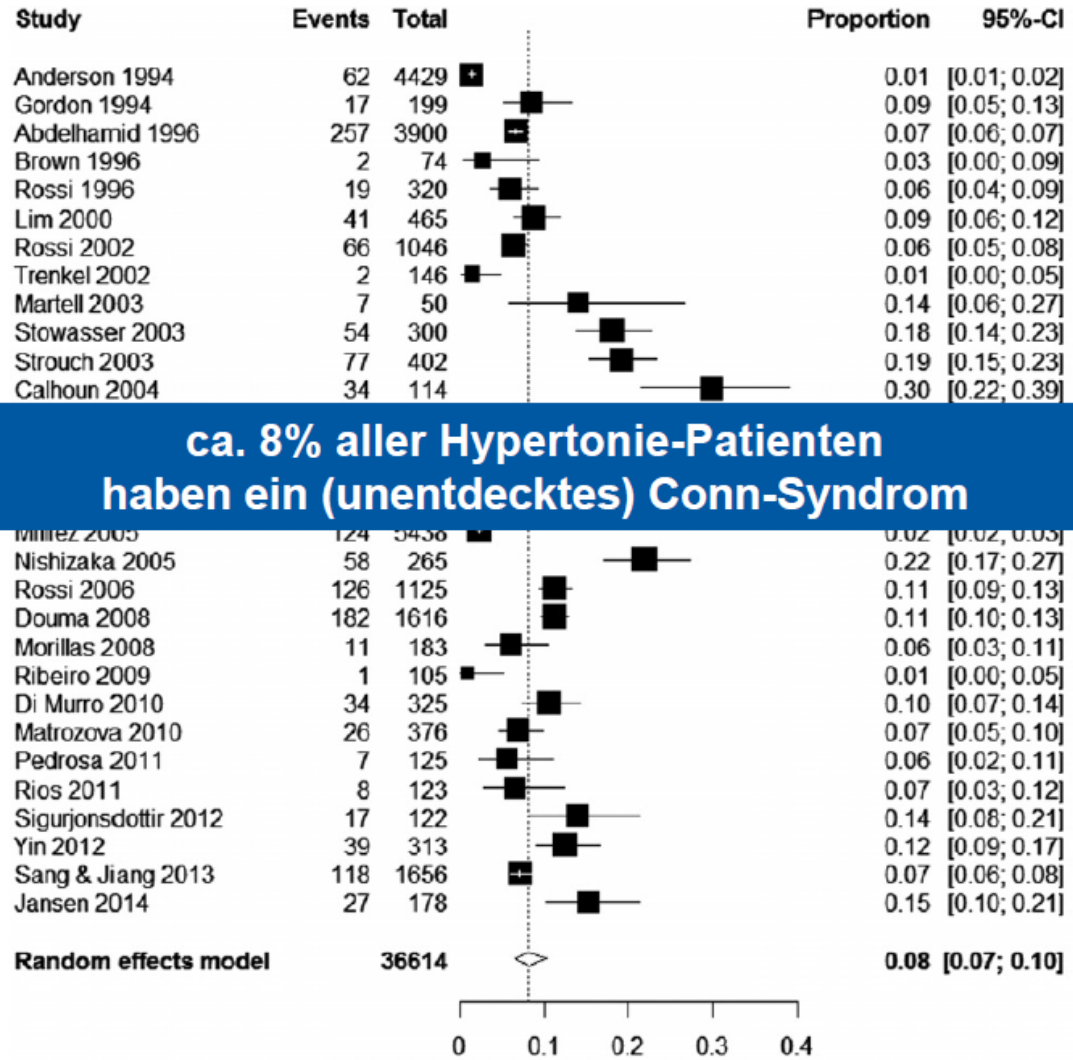
Endocrine Reviews, December 2018, 39(6):1057–1088

↓

Arterielle Hypertonie
Salzretention, Kaliumverlust
Renin-Suppression

Aldosteron inadäquat hoch für Salzhaushalt, relativ autonom bzgl. wesentlichen Regulatoren (Angiotensin, Kalium), nicht supprimierbar durch Salzbelastung

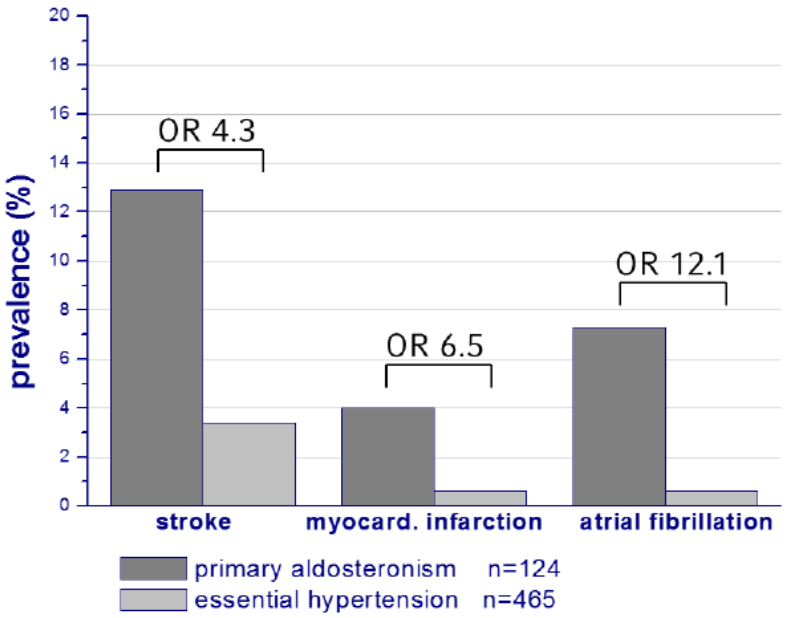
Meta-Analyse zur Prävalenz des PA

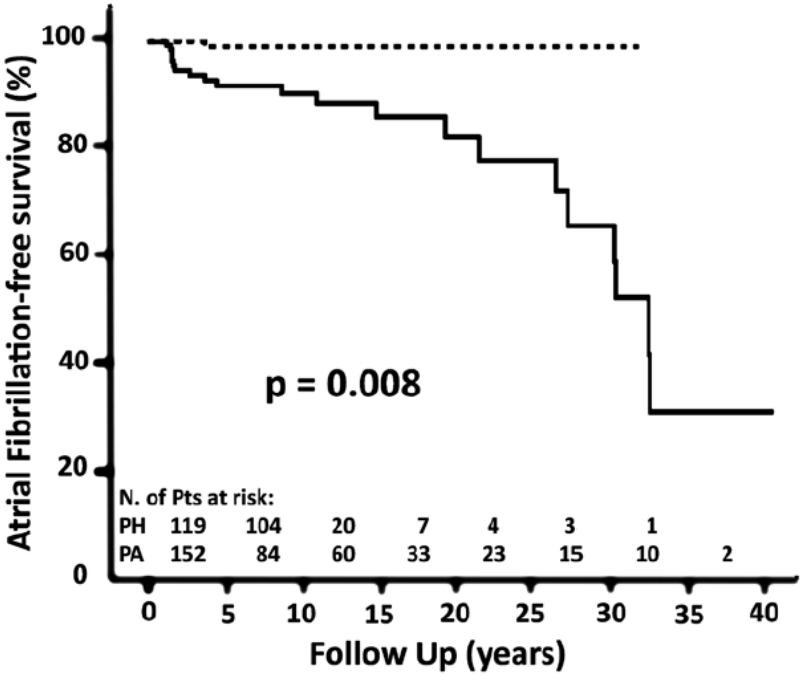


ca. 8% aller Hypertonie-Patienten haben ein (unentdecktes) Conn-Syndrom

Käyser SC et al. J Clin Endocrinol Metab. 2016 May 12

Kardiovaskuläre Komplikationen des Conn-Syndroms

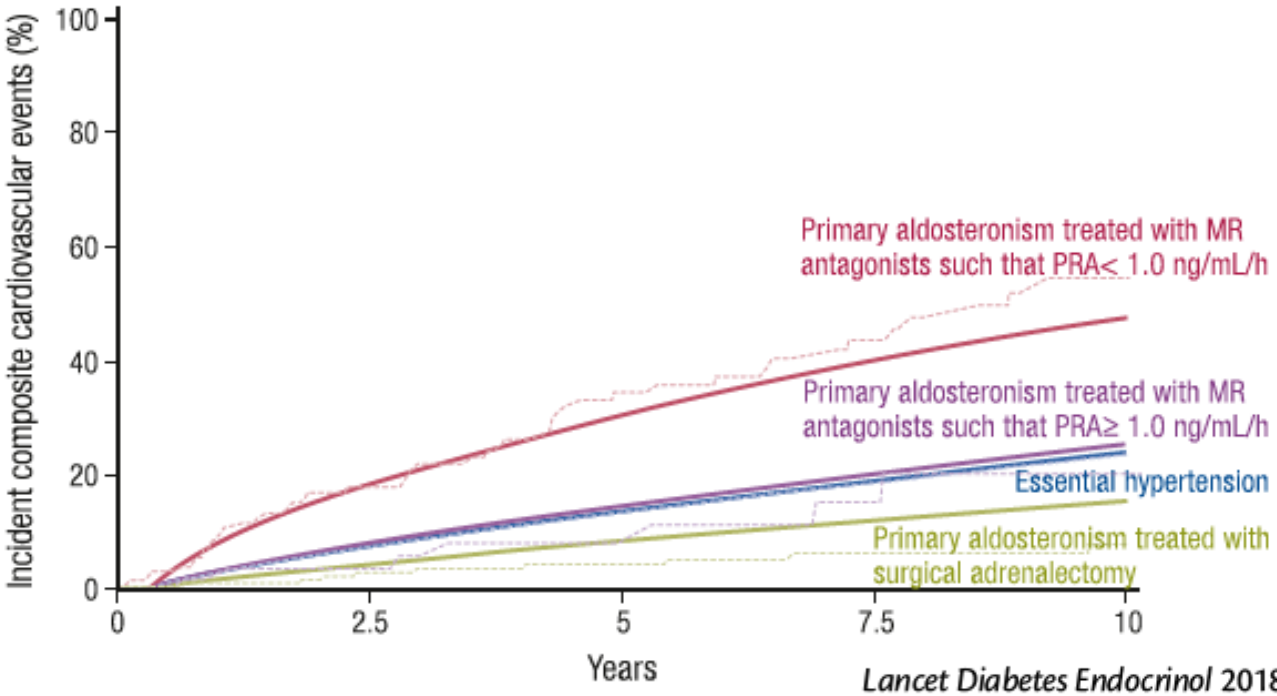




Milliez et al. J Am Coll Cardiol 2005; 45(8): 1249-50

Rossi GP et al. 2013 Hypertension 62, 62-69

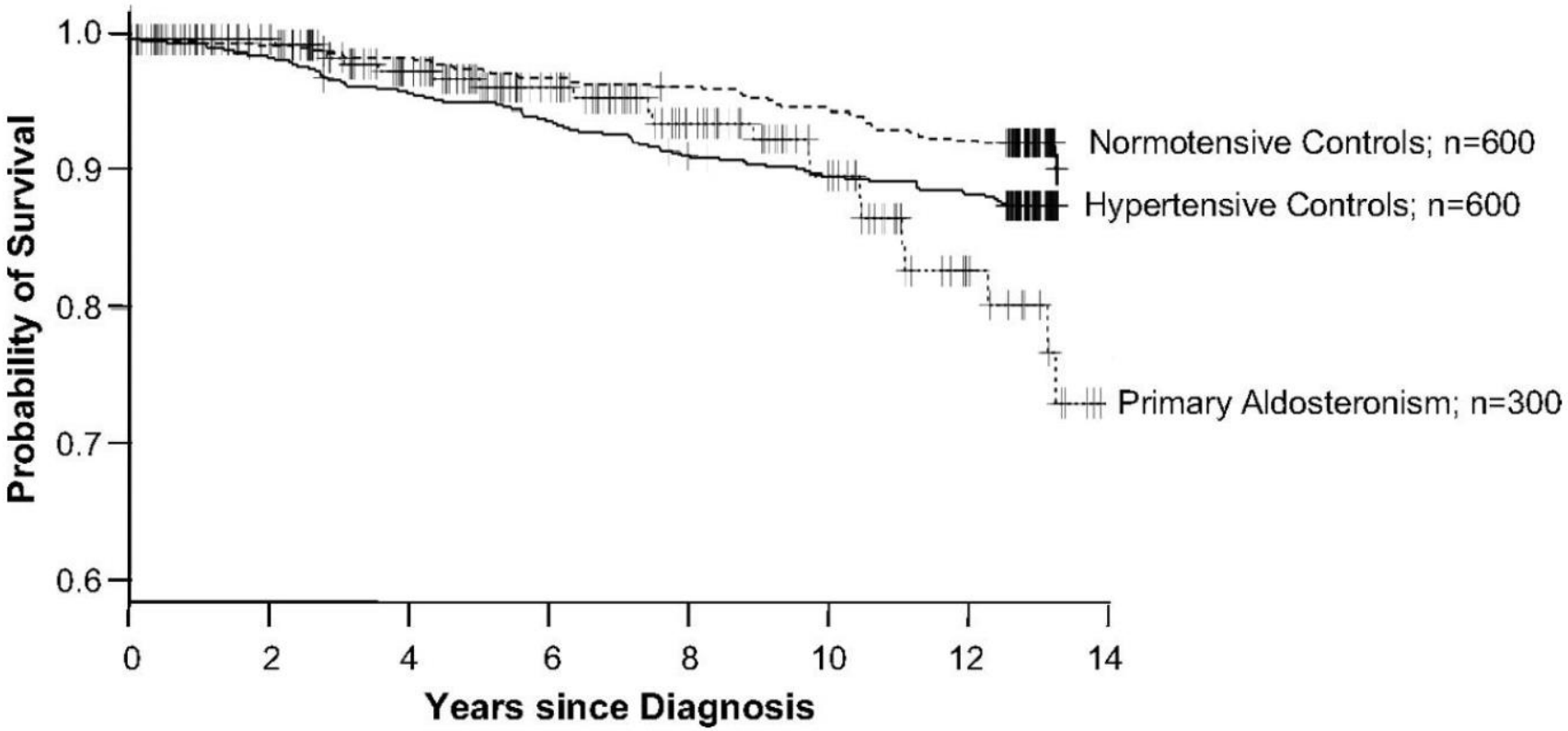
Kardiovaskuläre Ereignisse bei chirurgisch und medikamentös behandeltem Primären Hyperaldosteronismus



Lancet Diabetes Endocrinol 2018;6(1):51–59.

Langzeitmortalität bei Hyperaldosteronismus

(Daten aus dem deutschen Conn-Register)



Reincke M et al., Hypertension 2012; 60: 618-24

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

John W. Funder, Robert M. Carey, Franco Mantero, M. Hassan Murad, Martin Reincke, Hirotaka Shibata, Michael Stowasser, and William F. Young, Jr

Hudson Institute of Medical Research (J.W.F.), Clayton, VIC 3168, Australia; University of Virginia Health System (R.M.C.), Charlottesville, Virginia 22908; University of Padova (F.M.), 35122 Padua, Italy; Mayo Clinic, Evidence-based Practice Center (M.H.M.), Rochester, Minnesota 55905; Klinikum of the Ludwig-Maximilians-University of Munich (M.R.), 80366 München, Bavaria, Germany; Oita University (H.S.), Oita 870-1124, Japan; University of Queensland (M.S.), Brisbane, Australia; and Mayo Clinic (W.F.Y.), Rochester, Minnesota 55905

J Clin Endocrinol Metab, May 2016, 101(5):1889–1916

Wann screenen?

- **Case-detection:**
  - konstant erhöhter Blutdruck >150/100mmHg
  - Therapie-resistente Hypertonie
  - Hypertonie unter 4 oder mehr Antihypertensiva
  - Hypertonie mit Hypokaliämie
  - Hypertonie mit Schlafapnoe
  - Hypertonie mit Nebenniereninzidentalom
  - Hypertonie mit pos. Familienanamnese für frühzeitige Hypertonie oder zerebrovask. Ereignisse <40 Lj.
  - Hypertonie und erstgradige Verwandtschaft mit prim. Hyperaldosteronismus

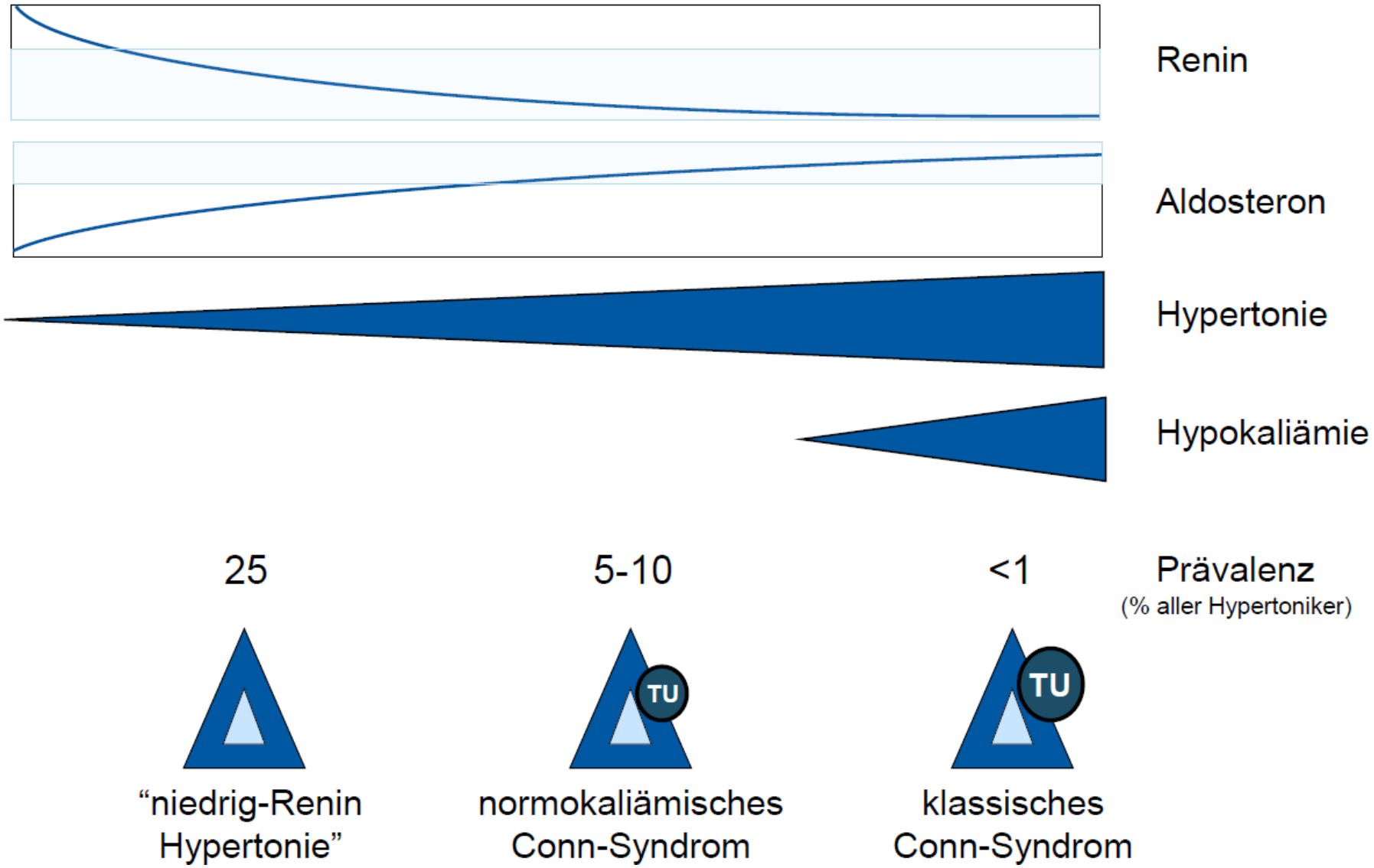
Wann screenen?

- **Case-detection:** **Prävalenz**
  - konstant erhöhter Blutdruck >150/100mmHg 8-13%
  - Therapie-resistente Hypertonie 17-23%
  - Hypertonie unter 4 oder mehr Antihypertensiva
  - Hypertonie mit Hypokaliämie
  - Hypertonie mit Schlafapnoe 34%
  - Hypertonie mit Nebenniereninzidentalom 2%
  - Hypertonie mit pos. Familienanamnese für frühzeitige Hypertonie oder zerebrovask. Ereignisse <40 Lj.
  - Hypertonie und erstgradige Verwandtschaft mit prim. Hyperaldosteronismus

Wann screenen?

- **Case-detection:**
  - konstant **erhöhter Blutdruck** >150/100mmHg
  - Therapie-resistente **Hypertonie**
  - **Hypertonie** unter 4 oder mehr Antihypertensiva
  - **Hypertonie** mit Hypokaliämie
  - **Hypertonie** mit Schlafapnoe
  - **Hypertonie** mit Nebenniereninzidentalom
  - **Hypertonie** mit pos. Familienanamnese für frühzeitige Hypertonie oder zerebrovask. Ereignisse <40 Lj.
  - **Hypertonie** und erstgradige Verwandtschaft mit prim. Hyperaldosteronismus

Kein Screening ohne Hypertonie



F. Beuschlein, 2018

Diagnostik

- Screening mit Aldosteron-Renin-Ratio (ARR)
- Störfaktoren:

- Abnahme ideal vormittags, nachdem Pat. ca. 2 Std. «auf den Beinen»
- 10-15min sitzen

Table 3. Factors That May Lead to False-Positive or False-Negative ARR Results

Factor	Effect on Aldosterone Plasma Levels	Effect on Renin Levels	Effect on ARR
Medications[a]			
β-Adrenergic blockers	D	D D	U (FP)
Central agonists (eg, clonidine, α-methyldopa)	D	D D	U (FP)
NSAIDs	D	D D	U (FP)
K^+-wasting diuretics	R U	U U	D (FN)
K^+-sparing diuretics	U	U U	D (FN)
ACE inhibitors	D	U U	D (FN)
ARBs	D	U U	D (FN)
Ca^{2+} blockers (DHPs)	R D	U	D (FN)
Renin inhibitors	D	D U	U (FP) D (FN)
Potassium status			
Hypokalemia	D	R U	D (FN)
Potassium loading	U	R D	U
Dietary sodium			
Sodium restriction	U	U U	U (FN)
Sodium loading	D	D D	U (FP)
Advancing age	D	D D	U (FP)
Premenopausal women (vs males)[b]	R U	D	U (FP)
Other conditions			
Renal impairment	R	D	U (FP)
PHA-2	R	D	U (FP)
Pregnancy	U	U U	D (FN)
Renovascular HT	U	U U	D (FN)
Malignant HT	U	U U	D (FN)

Table 4. Measurement of ARR: A Suggested Approach

A. Preparation: agenda
1. Attempt to correct hypokalemia. Measure plasma potassium in blood collected slowly with a syringe and needle [preferably not a Vacutainer to minimize the risk of spuriously raising potassium]. During collection, avoid fist clenching, wait at least 5 seconds after tourniquet release (if used) to achieve insertion of needle, and ensure separation of plasma from cells within 30 minutes of collection. A plasma [K^+] of 4.0 mmol/L is the aim of supplementation.
2. Encourage patient to liberalize (rather than restrict) sodium intake.
3. Withdraw agents that markedly affect the ARR (219) for at least 4 weeks:
   a. Spironolactone, eplerenone, amiloride, and triamterene
   b. Potassium-wasting diuretics
   c. Products derived from licorice root (eg, confectionary licorice, chewing tobacco)
4. If the results of ARR after discontinuation of the above agents are not diagnostic, and if hypertension can be controlled with relatively noninterfering medications (see Table 5), withdraw other medications that may affect the ARR (219) for at least 2 weeks, such as:
   a. β-Adrenergic blockers, central α-2 agonists (eg, clonidine, α-methyldopa), and nonsteroidal anti-inflammatory drugs
   b. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, and dihydropyridine calcium channel antagonists
5. If necessary to maintain hypertension control, commence other antihypertensive medications that have lesser effects on the ARR (*e.g.* verapamil slow-release, hydralazine [with verapamil slow-release, to avoid reflex tachycardia], prazosin, doxazosin, terazosin; see Table 5).
6. Establish OC and HRT status because estrogen-containing medications may lower DRC and cause false-positive ARR when DRC (rather than PRA) is measured (220). Do not withdraw OC unless confident of alternative effective contraception.

B. Conditions for blood collection
1. Collect blood midmorning, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes.
2. Collect blood carefully, avoiding stasis and hemolysis (see A.1 above).
3. Maintain sample at room temperature (and not on ice, as this will promote conversion of inactive to active renin) during delivery to laboratory and prior to centrifugation and rapid freezing of plasma component pending assay.

C. Factors to take into account when interpreting results (see Table 3)
1. Age: in patients aged >65 years, renin can be lowered more than aldosterone by age alone, leading to raised ARR.
2. Gender: premenstrual, ovulating females have higher ARR levels than age-matched men, especially during the luteal phase of the menstrual cycle, during which false positives can occur, but only if renin is measured as DRC and not as PRA (220).
3. Time of day, recent diet, posture, and length of time in that posture
4. Medications
5. Method of blood collection, including any difficulty doing so
6. Level of potassium
7. Level of creatinine (renal failure can lead to false-positive ARR)

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STOP für mind. 4 Wochen

4. If the results of ARR after discontinuation of the above agents are not diagnostic, and if hypertension can be controlled with relatively noninterfering medications (see Table 5), withdraw other medications that may affect the ARR (219) for at least 2 weeks, such as:
   a. β-Adrenergic blockers, central α-2 agonists (e ... ti-inflammatory drugs
   b. Angiotensin-converting enzyme inhibitors, an ... dihydropyridine calcium channel antagonists

STOP für mind. 2 Wochen

5. If necessary to maintain hypertension control, commence other antihypertensive medications that have lesser effects on the ARR (*e.g.* verapamil slow-release, hydralazine [with verapamil slow-release, to avoid reflex tachycardia], prazosin, doxazosin, terazosin; see Table 5)
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Hormonelle Kontrazeptiva?

B. Conditions for blood collection
1. Collect blood midmorning, after the patient has been up (sitting, standing, or walking) for at least 2 hours and seated for 5–15 minutes.
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Interpretation ARR

Table 6. ARR Cutoff Values, Depending on Assay and Based on Whether PAC, PRA, and DRC Are Measured in Conventional or Système International (SI) Units

	Renin → PRA, ng/mL/h	PRA, pmol/L/min	DRC, mU/L[a]	DRC, ng/L[a]
Aldosteron PAC (as ng/dL)	20	1.6	2.4	3.8
	30[b]	2.5	3.7	5.7
	40	3.1	4.9	
PAC (as pmol/L)	750[b]	60	91	144
	1000	80	122	192

[a] Values shown are on the basis of a conversion factor of PRA (ng/mL/h) to DRC (mU/L) of 8.2. DRC assays are still in evolution, and in a recently introduced and already commonly used automated DRC assay

60

Limitationen: sehr abhängig vom Renin, insb. im tiefen Bereich
→ tw. erhöhte ARR bei tiefem Aldosteron
Minimum-Aldosteron 410 pmol/l ? 280 pmol/l ?
Minimum-Renin von 4mU/l ?

conventional units).

Table 2. Criteria and Interpretations of Biochemical Screening Results for Primary Aldosteronism

Criteria	ARR, ng/dL per ng/mL/h	Serum Aldosterone, ng/dL	Plasma Renin Activity, ng/mL/h	Comments
Most conservative	≥40	≥20 555pmol/l	≤0.50	Highest risk of missing mild-to-moderate severity cases (*i.e.*, more false-negatives)
Conservative and most widely accepted	≥30	≥15 416pmol/l	≤1.0	Some risk of false-negatives
More permissive but less widely accepted	≥20 or ≥25	≥9–10	≤1.0	Some risk of false-positives
Most permissive	≥20	≥6	≤0.50	Highest risk of positive screens that are not true cases (*i.e.*, more false-positives)

Endocrine Reviews, December 2018, 39(6):1057–1088

BLUT-CHEMIE

		20.12.2012 0191 20.12.2012
Probenmaterial/Präanalytik:		
Befund telefonieren		
Heparin-Blut		×
Nativ-Blut		×
EDTA-Blut 4°		×
Bemerkung		
Serum		
Entnahme:		
nach	[min.]	
Natrium	[130-145 mmol/l]	137
Kalium	[3.5-5.1 mmol/l]	3.3
Creatinin	[<95 µmol/l]	61
Renin, aktives:[1]	[ng/l]	1.5
nach Ruhe	[3.0-28 ng/l]	
nach Belastung	[4.2-46 ng/l]	
Aldosteron:[1]	[pmol/l]	1340.0
liegend	[27-444 pmol/l]	
stehend	[111-860 pmol/l]	
Cortisol	[nmol/l]	

ARR 893

Renin, direkt	[mIU/l]	<0.5	1.85
liegend	[2.8-39.9 mIU/l]		
stehend	[4.4-46.1 mIU/l]		
Aldosteron	[pmol/l]	247	318

ARR 500 / 172

labormedizinisches zentrum
centre des laboratoires médicaux
centro medicina di laboratorio

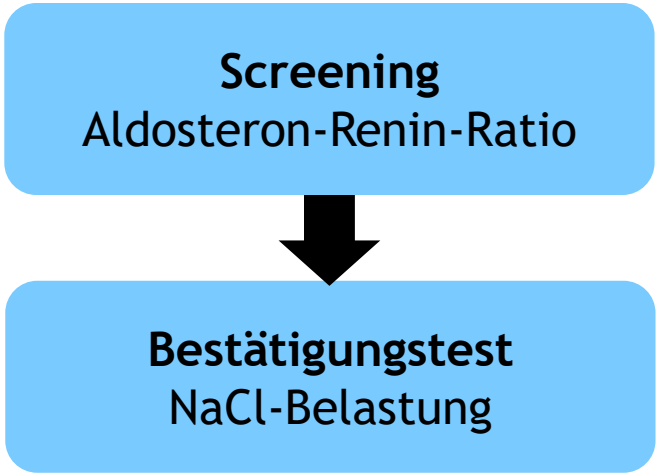
Dr Risch

ARR 35

ENDOKRINOLOGIE

ACTH [i]	9.6	pmol/l	1.3 - 13.9		
Aldosteron (CLIA)	309.0	pmol/l	87.3 - 474.5 61.2 - 977.8 (stehend)		
Renin (CLIA)	8.8	mU/L	2.5 - 42.0 4.4 - 46.1 (stehend)	5.9	(02.12.19)
Aldosteron/Renin Quotient *	21		< 19	*40	(02.12.19)

Unter Einhaltung der korrekten Präanalytik und Patientenvorbereitung weist ein ARQ >19 (Einheit ng/L / ng/L) beim Vorliegen einer Aldosteron-Erhöhung für die Entdeckung eines primären Hyperaldosteronismus eine Sensitivität von 98% bei einer Spezifität von 91% auf. Informationen zur Präanalytik und Patientenvorbereitung siehe Riport 81.


Screening
Aldosteron-Renin-Ratio
Bestätigungstest
NaCl-Belastung

Bestätigungstest

- **NaCl-Infusion**
  - **Aldosteron vor und nach 2 L NaCl-Infusion über 4 Std.**
  - **physiologisch: Aldosteron-Suppression <140 pmol/l**
  - **pathologisch (i.S. Bestätigung): Aldosteron >280 pmol/l**
  - **(bei Test im Sitzen: Aldosteron pathologisch >170 pmol/l)**
- orale NaCl-Belastung
- Captopril-Test
- Fludrocortison-Test

verzichtbar bei eindeutiger Situation:

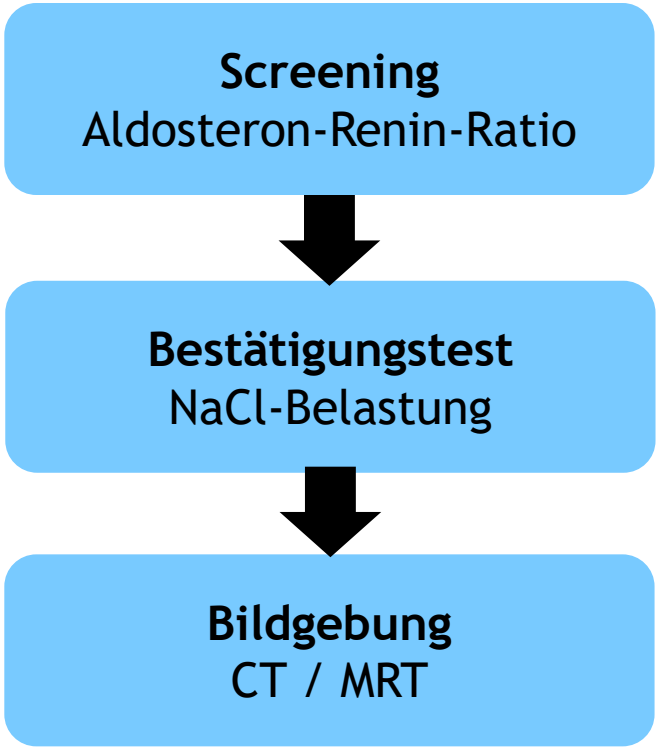
Aldosteron >550pmol/l

Renin supprimiert

Hypokalämie

BLUT-CHEMIE

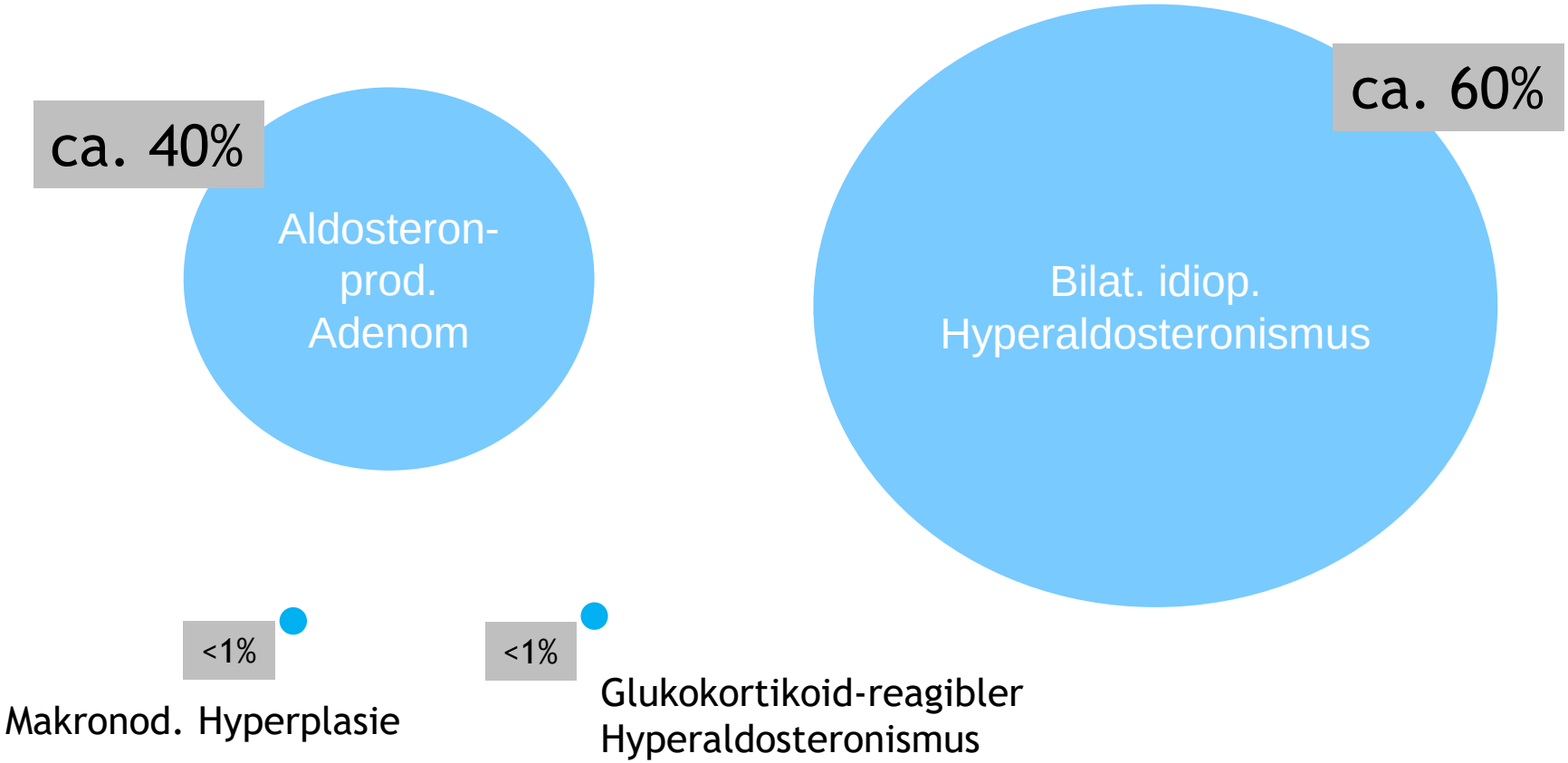
	24.5.2018 0008 24.5.2018 07:45	24.5.2018 0124 24.5.2018 12:00
Labor	ZLM SG	ZLM SG
Probenmaterial/Präanalytik:		
Heparin-Blut	×	×
EDTA-Blut	×	
Nativ-Blut	×	×
Entnahme:		
nach [min.]		240
Kalium [3.5-5.1 mmol/l]	3.1	
Glucose (nü) [3.9-5.6 mmol/l]	8.7	
Renin, direkt [mIU/l]	11.6	
liegend [2.8-39.9 mIU/l]		
stehend [4.4-46.1 mIU/l]		
Aldosteron [pmol/l]	997	537
liegend [48.7-642.6 pmol/l]		
stehend [69.8-1085.8 pmol/l]		

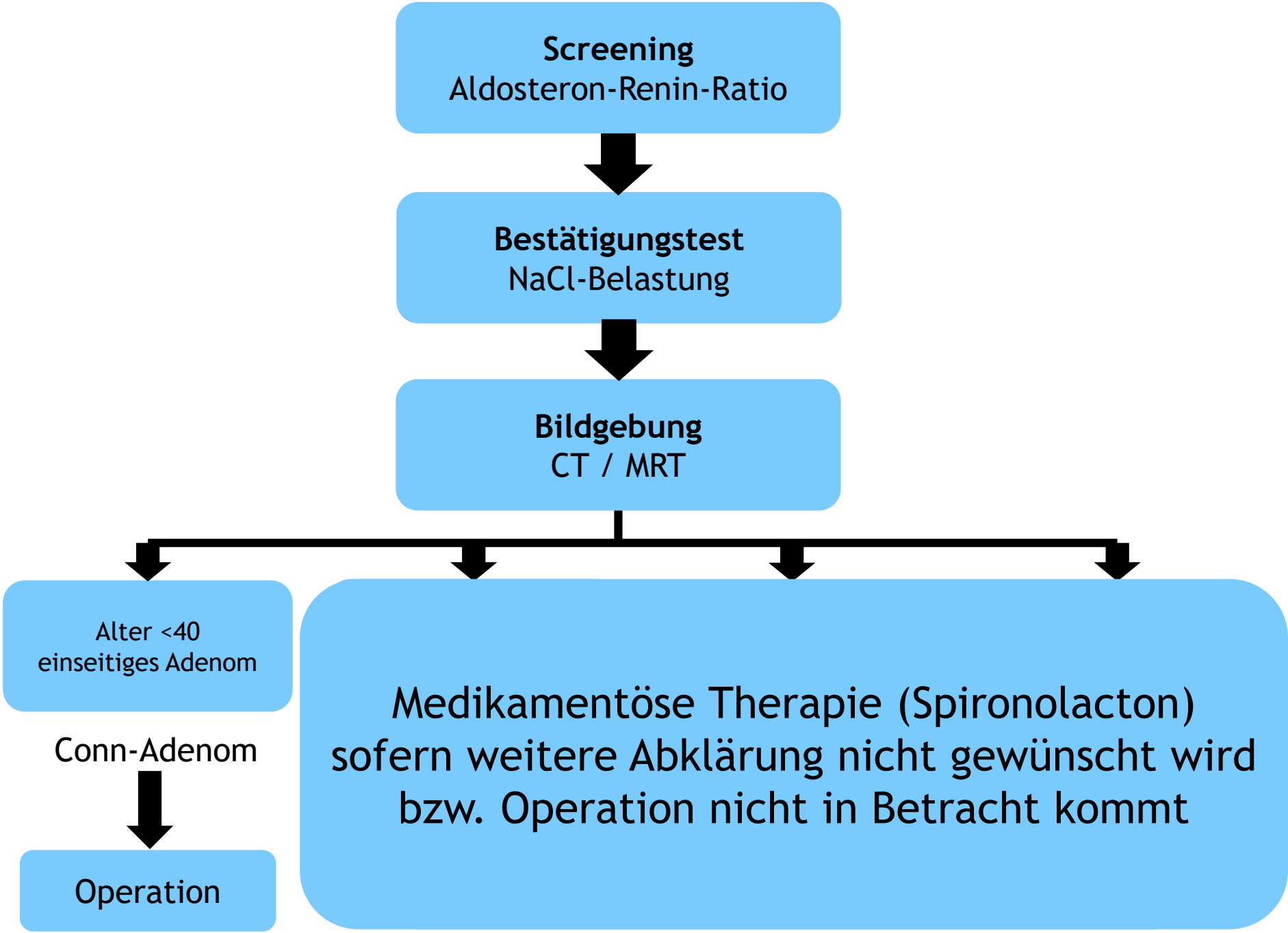

Screening
Aldosteron-Renin-Ratio
Bestätigungstest
NaCl-Belastung
Bildgebung
CT / MRT

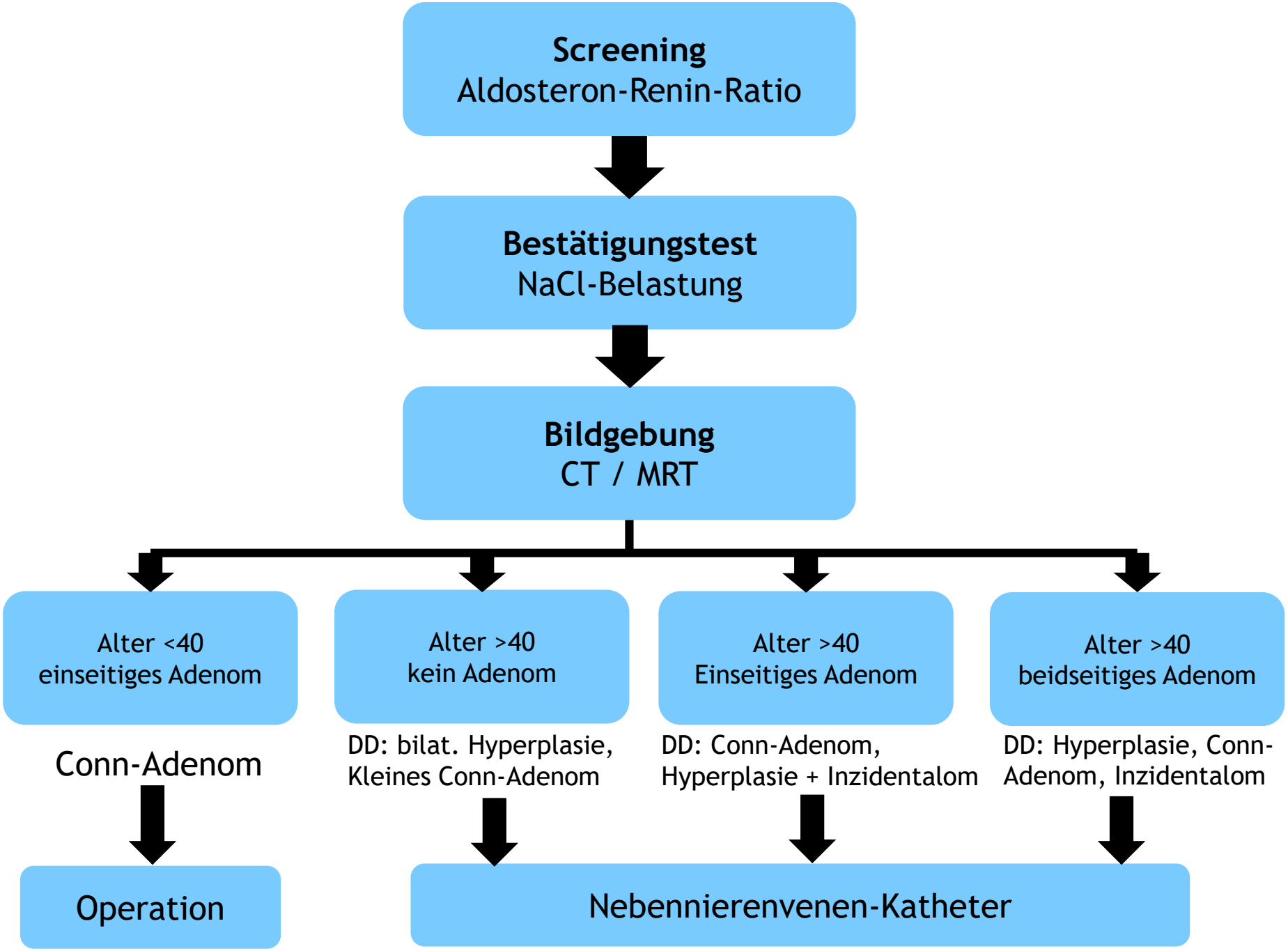
Differentialdiagnose

Ausschluss adrenocorticales Karzinom

Subtyp-Klassifizierung




Screening
Aldosteron-Renin-Ratio
Bestätigungstest
NaCl-Belastung
Bildgebung
CT / MRT
Alter <40
einseitiges Adenom
Conn-Adenom
Operation
Medikamentöse Therapie (Spironolacton)
sofern weitere Abklärung nicht gewünscht wird
bzw. Operation nicht in Betracht kommt


Screening
Aldosteron-Renin-Ratio
Bestätigungstest
NaCl-Belastung
Bildgebung
CT / MRT
Alter <40
einseitiges Adenom
Alter >40
kein Adenom
Alter >40
Einseitiges Adenom
Alter >40
beidseitiges Adenom
Conn-Adenom
DD: bilat. Hyperplasie,
Kleines Conn-Adenom
DD: Conn-Adenom,
Hyperplasie + Inzidentalom
DD: Hyperplasie, Conn-
Adenom, Inzidentalom
Operation
Nebennierenvenen-Katheter

Nebennierenvenen-Sampling

Lukas Hechelhammer
Klinik für Radiologie und Nuklearmedizin
Kantonsspital St. Gallen

Uni- oder bilaterale Aldosteronproduktion?

- CT / (MRI) Pitfalls
  - Nur 62% Übereinstimmung falls CT und NNV-Sampling

Concordance	CT bilateral, AVS unilateral	CT unilateral, AVS bilateral	CT and AVS unilateral but opposite
62.2% (591/950)	19.2% (182/950)	14.7% (140/950)	3.9% (37/950)

  - Tiefe Sensitivität für Adenome < 1cm
  - Tiefe Sensitivität für unilaterale Hyperplasie
  - 90% der Incidentalome sind „nicht-sekretierend“

Kempers MJ et al. Ann Intern Med 2009
Sherlock M et al. Endocr Rev 2020

Unilaterale Adrenalektomie nach NNV-Sampling

Study	Rate of biochemical cure
Umakoshi (Umakoshi et al. 2018)	81.0% (187/231)
SPARTICUS (Dekkers et al. 2016)	88.1% (37/42)
AVIS-2 (Rossi et al. 2019)	93.8% (487/519)
Laurder (Ladurner et al. 2017)	95.9% (142/148)
Lim (Lim et al. 2014)	96.5% (112/116)
Citton (Citton et al. 2015)	100% (56/56)
Pasternak (Pasternak et al. 2016)	100% (45/45)

Quencer KB CVIR Endovascular 2021

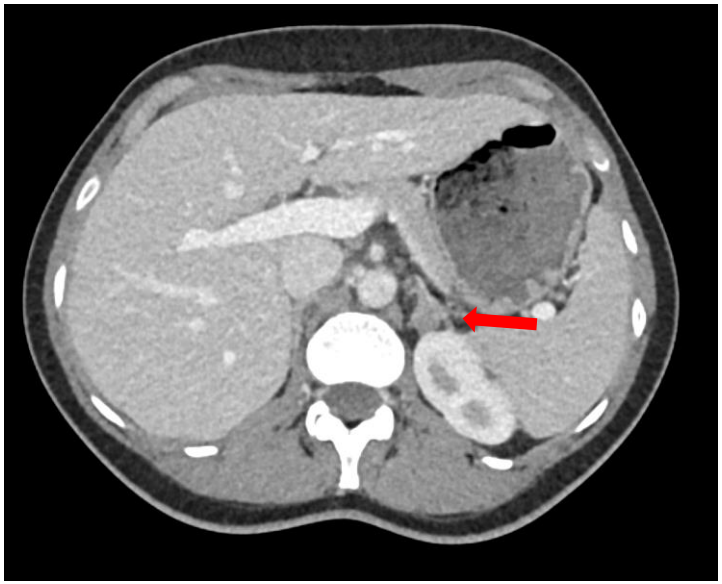
Schnittbildgebung

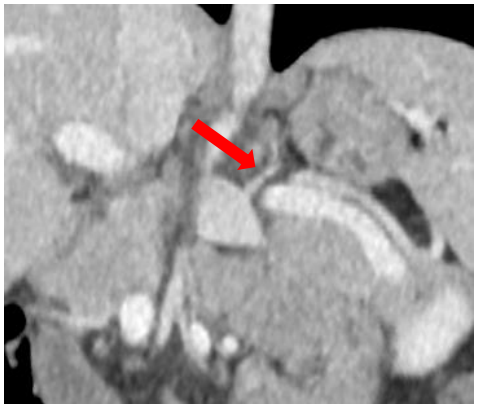
- CT mit KM (portal-venöse Phase)
  - Gute Sichtbarkeit der rechten NNV
  - Lipid-arme Adenome besser charakterisierbar (wash-out)
  - Bessere Auflösung für kleinere Adenome

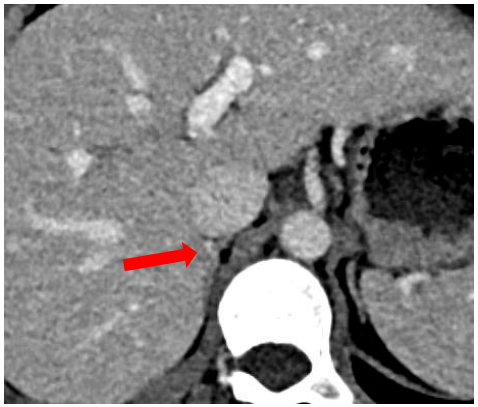
- MRI mit KM

- Darstellung der NN bds.
- Darstellung der NN-Venen

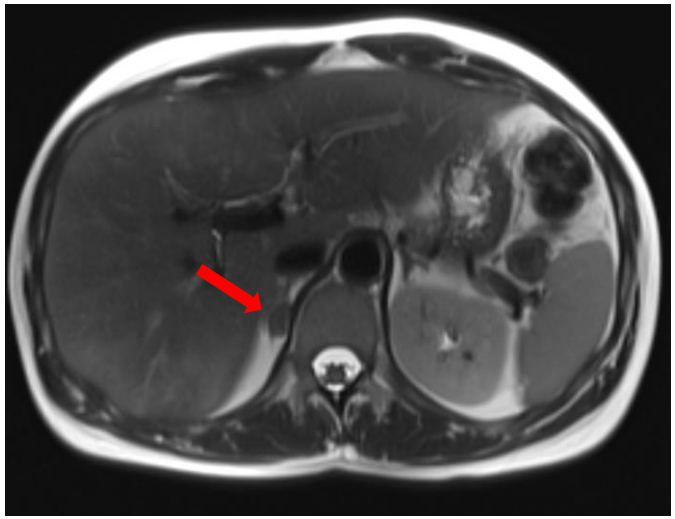
CT

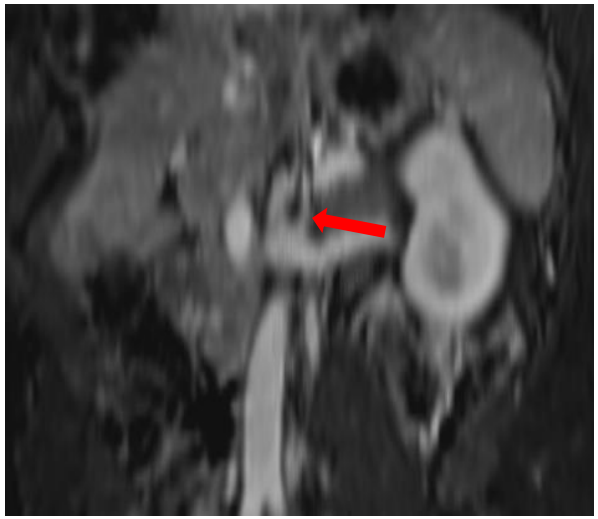


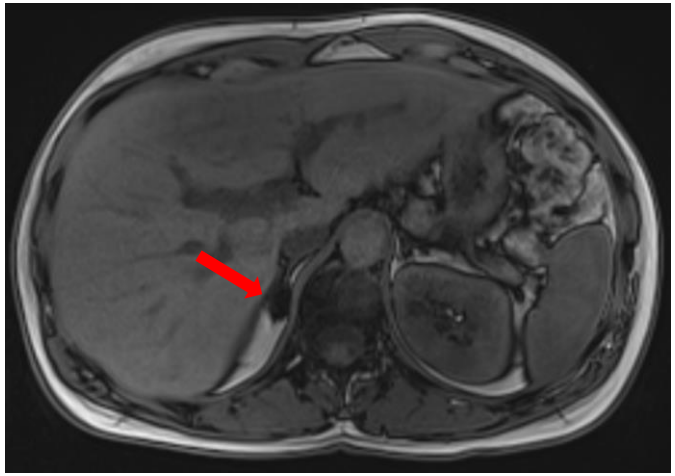


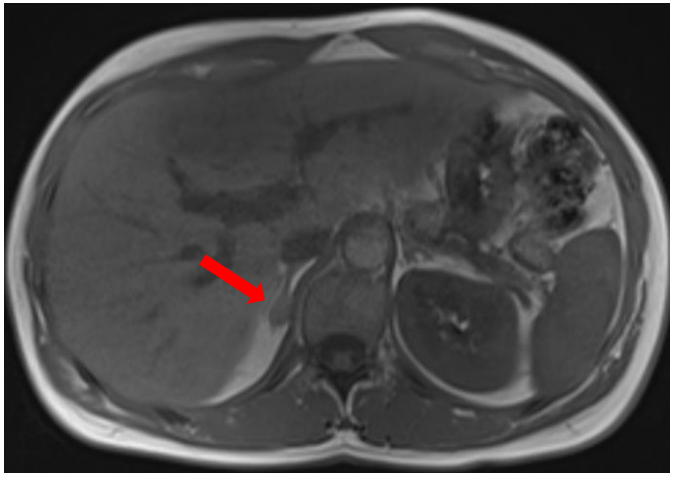


MRI



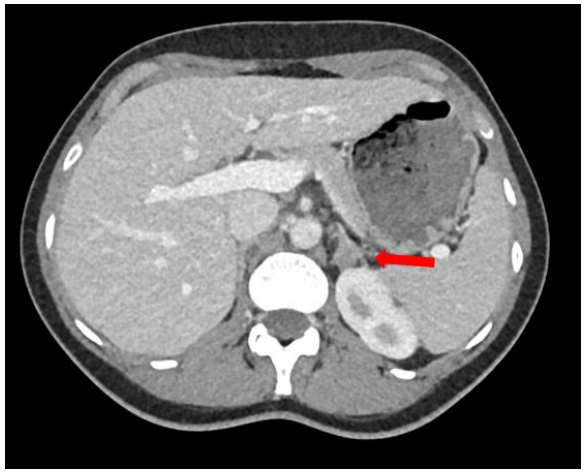


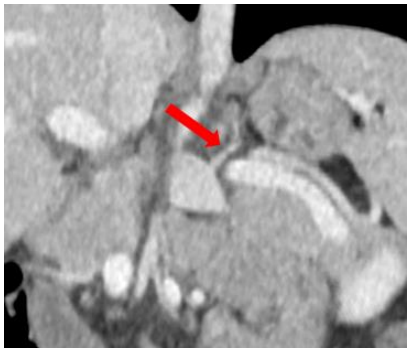


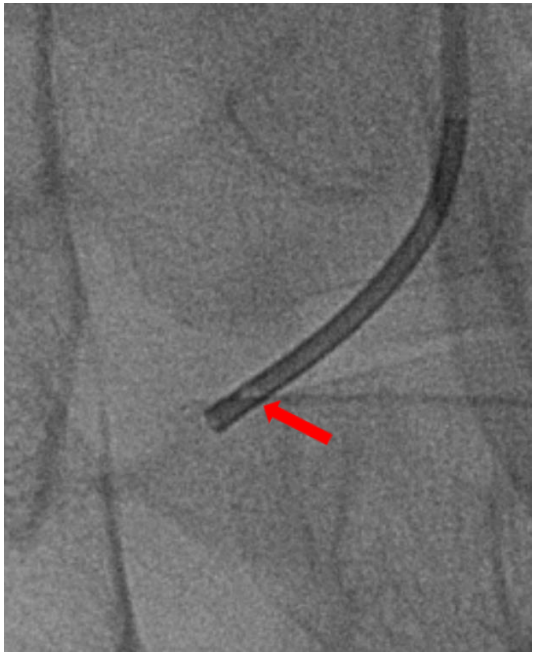


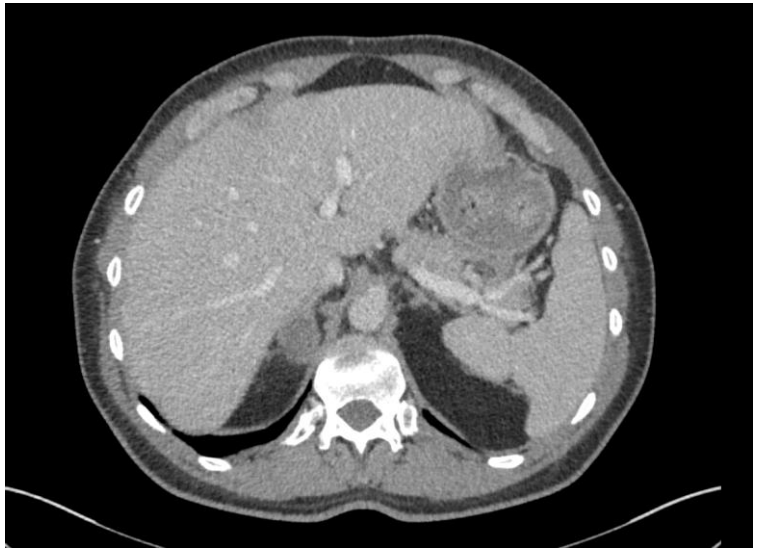
NNV-Sampling

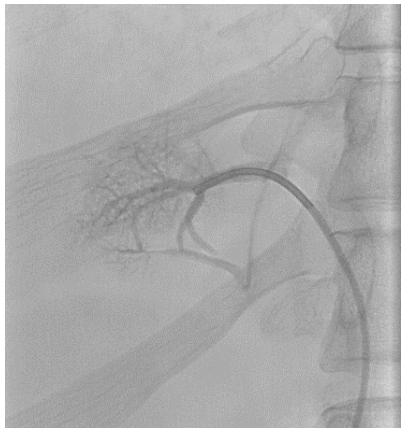
- Schleuse V.femoralis communis
- 5000E Heparin
- Selektive Katheterisierung der linken und rechten NN-Vene

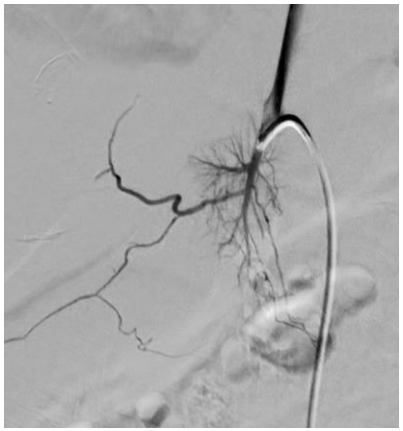












Komplikationen

- NN-Blutung (erschwert Operation)
- Infarkt (kann Operation „ersetzen“)
- Hypertensive Krise

- Ältere Publikationen bis zu 10%
- Aktuell < 1%

Quencer KB CVIR Endovasular 2021
Fischer CE et al. NEJM 1971

BLUT-CHEMIE

	6509 KSSG3708S 15.05.2019 13:00	6513 KSSG3708S 15.05.2019 17:00	22. 5.2019 0040 22.5. 08:32	22. 5.2019 0041 22.5. 08:32	22. 5.2019 0042 22.5. 08:32	22. 5.2019 0043 22.5.2019 08:46	22. 5.2019 0044 22.5.2019 08:46	22. 5.2019 0045 22.5.2019 08:46
Labor	ZLM SG	ZLM SG	ZLM SG	ZLM SG	ZLM SG	ZLM SG		ZLM SG
Probeneingang								
Datum	15.Mai	15.Mai	×	×	×	×	×	×
Zeit	13:58	19:50	×	×	×	×	×	×
Probenmaterial/Präanalytik:								
Befund telefonieren			2697	2697		2697	2697	
Heparin-Blut			×	×		×	×	
Citrat-Blut	×							
Nativ-Blut					×			×
EDTA-Plasma								
Heparin-Plasma								
Serum		×						
Bemerkung			peripher	NNV li	NNV li	peripher	NNV re	NNV re
Serothek [Tage]					5			5
Natrium [136-144 mmol/l]								
Kalium [3.5-5.1 mmol/l]								
Chlorid [95-113 mmol/l]								
Calcium [2.0-2.6 mmol/l]								
Phosphat [0.8-1.5 mmol/l]								
Harnstoff [2-8 mmol/l]								
Creatinin [<95 µmol/l]								
Harnsäure [150-360 µmol/l]								
Bilirubin gesamt [<20 µmol/l]								
Total Proteine [63-83 g/l]								
CRP [<8 mg/l]								
Mittl. Blutzuckerwert [mmol/l]	6.2							
HbA1c [4.0-5.7 %]	5.5							
Renin, direkt [mIU/l]								
liegend [2.8-39.9 mIU/l]								
stehend [4.4-46.1 mIU/l]								
Aldosteron [pmol/l]		265			61000			12000
liegend [48.7-642.6 pmol/l]								
stehend [69.8-1085.8 pmol/l]								
Cortisol [nmol/l]			345	8181		429	14650	

Selektivitätsindex
Cortisol NN-Vene / peripher >2
→ korrekte Katheterlage

BLUT-CHEMIE

	6509 KSSG3708S 15.05.2019 13:00	6513 KSSG3708S 15.05.2019 17:00	22. 5.2019 0040 22.5. 08:32	22. 5.2019 0041 22.5. 08:32	22. 5.2019 0042 22.5. 08:32	22. 5.2019 0043 22.5.2019 08:46	22. 5.2019 0044 22.5.2019 08:46	22. 5.2019 0045 22.5.2019 08:46
Labor	ZLM SG	ZLM SG	ZLM SG	ZLM SG	ZLM SG	ZLM SG		ZLM SG
Probeneingang								
Datum	15.Mai	15.Mai	×	×	×	×	×	×
Zeit	13:58	19:50	×	×	×	×	×	×
Probenmaterial/Präanalytik:								
Befund telefonieren			2697	2697		2697	2697	
Heparin-Blut			×	×		×	×	
Citrat-Blut	×							
Nativ-Blut					×			×
EDTA-Plasma								
Heparin-Plasma								
Serum		×						
Bemerkung			peripher	NNV li	NNV li	peripher	NNV re	NNV re
Serothek [Tage]					5			5
Natrium [136-144 mmol/l]								
Kalium [3.5-5.1 mmol/l]								
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Cortisol [nmol/l]			345	8181		429	14650	

Lateralisationsindex
Aldosteron/Cortisol li/re >4:1
→ eindeutige Lateralisation

NNV-Sampling am KSSG seit 2013

Patient	ARR	CT	AVS-Lateralisation	remarks	outcome
1	>1000	Adenom li	li (>400)		ADX
2	893	Adenom li	-	missed dilution	ADX
3	600	Adenom li	li (9.8)	adrenal infarction	MR-antagonist
4	173	Adenom li	re (24)		MR-antagonist
5	>1000	Adenom li	li (7)		ADX
6	211	Adenom re		selectivity index failed	ADX
7	234	Adenom re		missed dilution	ADX
8	105	Adenom re	no (1.2)		MR-antagonist
9	204	normal	no (3.8)	adrenal hemorrhage	MR-antagonist
10	693	Adenom li	li (17)		ADX
27	880	normal	no (0.9)		MR-antagonist
28	1740	Adenom bds.	re (>6)		
29	178	Adenom li	li (8)		ADX
30	500	Adenom li	no (1.1)		MR-antagonist
31	100	Adenom re	no (1.05)		MR-antagonist
32	253	Adenom re	re (15)		ADX
33	814	Adenom li	li (13)		ADX
34	166	Adenom li	no (1.5)		MR-antagonist
35	>1500	Adenom re	re (33)		ADX

30 / 35 mit eindeutigem Resultat
2 postinterventionelle Komplikationen
24 mit unilateralem Adenom
16 mit Adrenalektomie
13 mit diskordantem Befund von CT und Sampling

Therapie

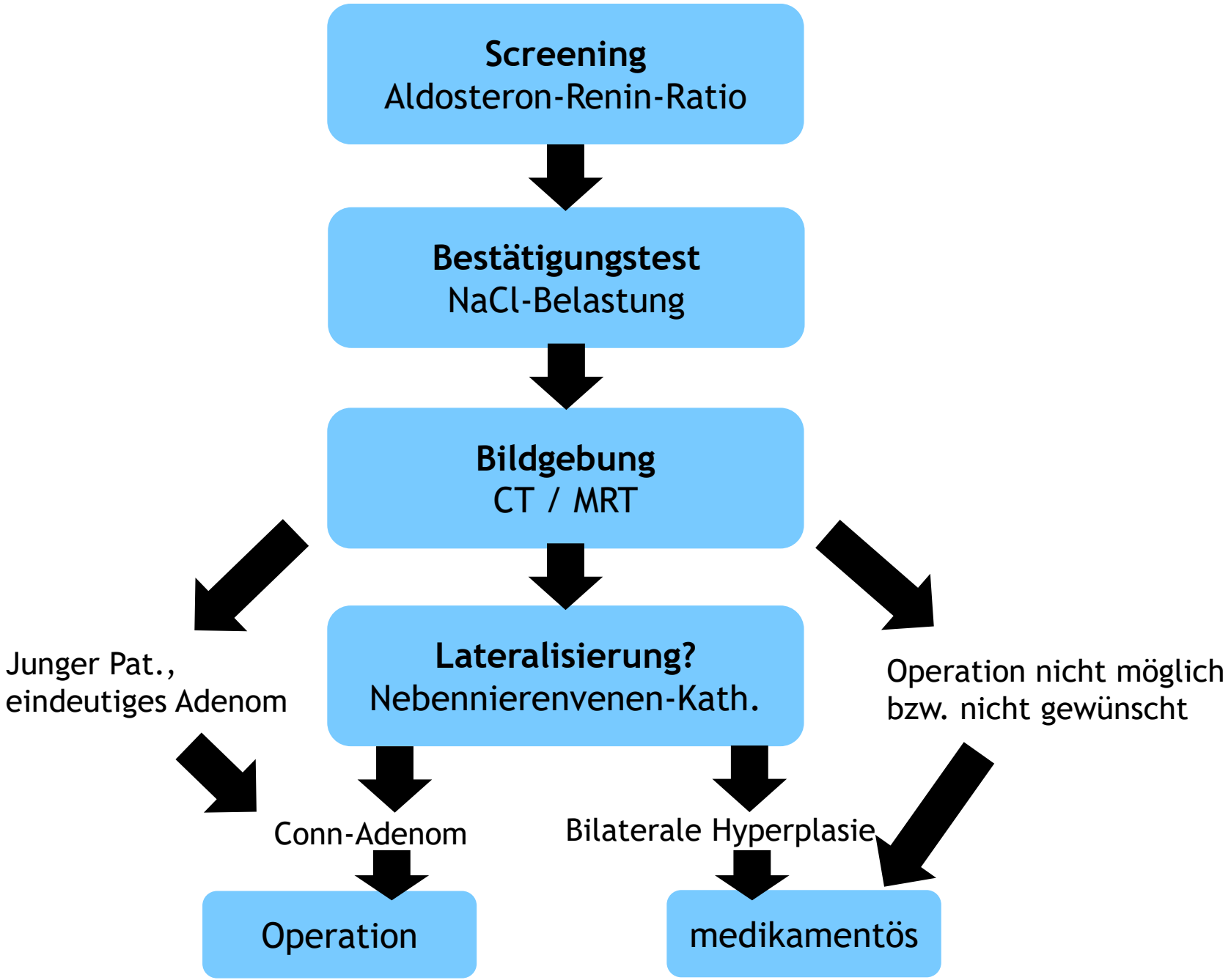
Conn-Adenom

- laparoskop. Adrenal-ektomie / Adenomexstir.
- Verbesserung von RR und Hypokaliämie 100%
- «Heilung» der Hypertonie 50% (d.h. keine antihypertensive Medikation mehr nötig)

Bilateraler idiopathischer Hyperaldosteronismus

- Mineralokortikoid-Rezeptor-Antagonist
- Spironolacton 25-200mg
- Epleronon 2x25 – 2x50mg

Ziel: Normalisierung von Blutdruck und Kalium
idealerweise auch Renin-Anstieg


Screening
Aldosteron-Renin-Ratio
Bestätigungstest
NaCl-Belastung
Bildgebung
CT / MRT
Lateralisierung?
Nebennierenvenen-Kath.
Junger Pat.,
eindeutiges Adenom
Operation nicht möglich
bzw. nicht gewünscht
Conn-Adenom
Bilaterale Hyperplasie
Operation
medikamentös