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Levels of angiotensin peptides in healthy and cardiovascular/renal-diseased paediatric population—an investigative review

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Abstract
The renin-angiotensin-aldosterone system (RAAS) plays a major role in the regulation of blood pressure and homeostasis. Therefore, it is a commonly used target for pharmacotherapy of cardiovascular diseases in adults. However, the efficacy of this pharmacotherapy can only be limitedly derived into children. Comprehensive knowledge of the humoral parameters acting in the paediatric RAAS (e.g. angiotensin I, angiotensin II, angiotensin 1–7, angiotensin III, and angiotensin IV) might facilitate a more effective and rational pharmacotherapy in children. Therefore, this review aims to provide an overview of the maturing RAAS. Out of 925 identified records, 35 publications were classified as relevant. Physiological and pathophysiological concentrations of angiotensin peptides were compiled and categorised according to European Medicines Agency age groups. Age has a major impact on circulating angiotensin I, angiotensin II, and angiotensin 1–7, which is reflected in an age-dependent decrease during childhood. In contrast to data obtained in adults, no gender-related differences in angiotensin levels were identified. The observed increase in peptide concentrations regarding cardiac- and renal-diseased children is influenced by surgical repair, while evidence for a pharmacological impact is conflicting. A comprehensive set of angiotensin I, angiotensin II, and angiotensin 1–7 values from neonates up to adolescents was compiled. Indicating age as a strong effector. However, evidence about potential promising targets of the RAAS like angiotensin III and angiotensin IV is still lacking in children.

Keywords RAAS · Angiotensin · Paediatric · Cardiovascular disease · Renal disease

Abbreviations

ACEi	Angiotensin-converting enzyme inhibitor
AGA	Appropriate for gestational age
ANCS	Antenatal corticosteroids
Ang	Angiotensin
ASD	Atrial septal defect
BDG	Bidirectional Glenn
CCB	Calcium channel blocker
CRF	Chronic renal failure
CVD	Cardiovascular disease
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ESRD	End-stage renal disease
GA	Gestational age
HPLC	High-pressure liquid chromatography
HUT	Head-up tilt
IQR	Interquartile range
LENA	Labeling of enalapril up to adolescents
MLBW	Moderate-low birthweight
NBW	Normal birthweight
RAAS	Renin-angiotensin-aldosterone system
RF	Renal failure
RIA	Radioimmunoassay
SD	Standard deviation
SE	Standard error
SGA	Small for gestational age
SRINS	Steroid-resistant idiopathic nephrotic syndrome
UV/VIS	Ultraviolet/visible spectroscopy
VLBW	Very low birthweight
VSD	Ventricular septal defect

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Introduction

The renin-angiotensin-aldosterone system (RAAS) is a major regulator of blood pressure, perfusion, and fluid haemostasis. It subsequently plays a key role in the development and prevalence of high blood pressure, renal failure (RF), and leading causes of death in the Western world, such as cardiovascular disease (CVD), including heart failure and coronary arterial diseases in adults [1].

Whereas the progress in pharmacological treatment of CVD and RF in adults strides ahead, studies show that pharmacotherapy in adults can be only limitedly transferred to children, based on the different aetiology (e.g. distinctive age-dependent variability in metabolism, expression of target structures and body composition) as well as alterations in the ontogeny of maturing children [2, 3]. The lack of efficacy suggests that the interaction of humoral parameters and their influence on significant endogenous systems like the RAAS are poorly understood in children.

The RAAS is described by an enzymatic cascade in which the inactive interims' peptide angiotensin I (AngI) is generated from angiotensinogen via renin and further processed via diverse enzymes to physiologically active products like angiotensin II (AngII), angiotensin 1–7 (Ang1–7), angiotensin III (AngIII), and angiotensin IV (AngIV) [4]. The current pharmacological strategies on the RAAS focus on the inhibition of the endogenous angiotensin peptides AngI, AngII and their target receptors. However, recent research focuses on AngIII, Ang1–7, and AngIV [4], which raises a controversial discussion whether AngI and AngII represent the most appropriate target structures or less-investigated peptides such as AngIII and Ang1–7 could be more suitable [5]. Since the efficacy of well-established pharmacotherapy is limited in children, these structures might represent promising targets for more effective therapy in the vulnerable population. Yet, the current data regarding circulating concentrations of angiotensin peptides in paediatric population is inconsistent, which highlights the need for a comprehensive evaluation of the maturing RAAS in order to facilitate future progress in paediatric care in all age groups.

The aim of this review is to give an overview of AngI, AngII, Ang1–7, AngIII, and AngIV values in healthy besides cardiovascular- and renal-diseased children to outline the current state of knowledge of the RAAS in childhood.

Methods

A literature search was conducted in the MEDLINE database via PubMed between August 2018 and January 2019. For record identification, the search term "(Angiotensin I OR Angiotensin II OR Angiotensin-(1–7) OR Angiotensin III OR Angiotensin IV) AND (Child OR infant OR newborn OR toddler)" was defined. Filter set was as follows: humans, German, English, and child (birth–18 years). Healthy children were defined as children without any cardiac and renal diseases or other ailments with known evidence for influencing the RAAS. CVD was defined as congenital or acquired heart defects including heart failure and dilated cardiomyopathy. The definition of subjects with RF in this literature search represents congenital or acquired nephrotic diseases including chronic kidney diseases (stages G2–G5) as well as patients after surgical treatment of the kidney. Overall, 928 findings were screened of which 35 publications were classified as relevant for this review. Inclusion criteria were human in vivo serum/plasma values of AngI, AngII, Ang1–7, AngIII, and AngIV in paediatrics from birth to 18 years of age. Further details are provided in the PRISMA diagram (Fig. 1).

Results

Age-related change of angiotensins during childhood

The ontogeny in children is related to various metabolic and enzymatic changes during childhood. Alteration in parameters occurs in different velocities, leading to constantly changing conditions in the organism [2, 3, 6]. Compiled data for angiotensins anticipate that angiotensin peptides decrease rapidly in newborns during the first weeks of life, but remain higher in childhood compared with adult concentrations (Table 1; Fig. 2).

If not otherwise indicated, statistical operators for age and plasma concentrations were expressed as range and mean ± standard deviation (SD), respectively.

Newborns

AngI values in newborns are reported by Fiselier et al. in the early 1980th only. The plasma concentrations of 9 newborns and infants (1 week–3 months) ranged from 191 to 468 pg/mL with a median of 302 pg/mL, which were higher than in older subjects (4 months–13 years) investigated in the same study [6].

Simultaneously measured AngII values revealed likewise higher concentration with a range of 30–117 pg/mL and a median of 58 pg/mL than in older subjects [6]. Pipkin et al. measured AngII concentrations in newborns with prematurity or jaundice. AngII levels significantly decreased from 178.4 ± 26.2 pg/mL (cord venous blood) at birth to 60.3 ± 9.2 pg/mL during the first 6 days but were higher than in adult controls (28.8 ± 4.2 pg/mL) [10]. Later on, the same group investigated AngII values in 46 healthy newborns 1–11 days after birth. Newborns with less than 4 days of age showed non-significant higher AngII levels than newborns more than 4 days of age.

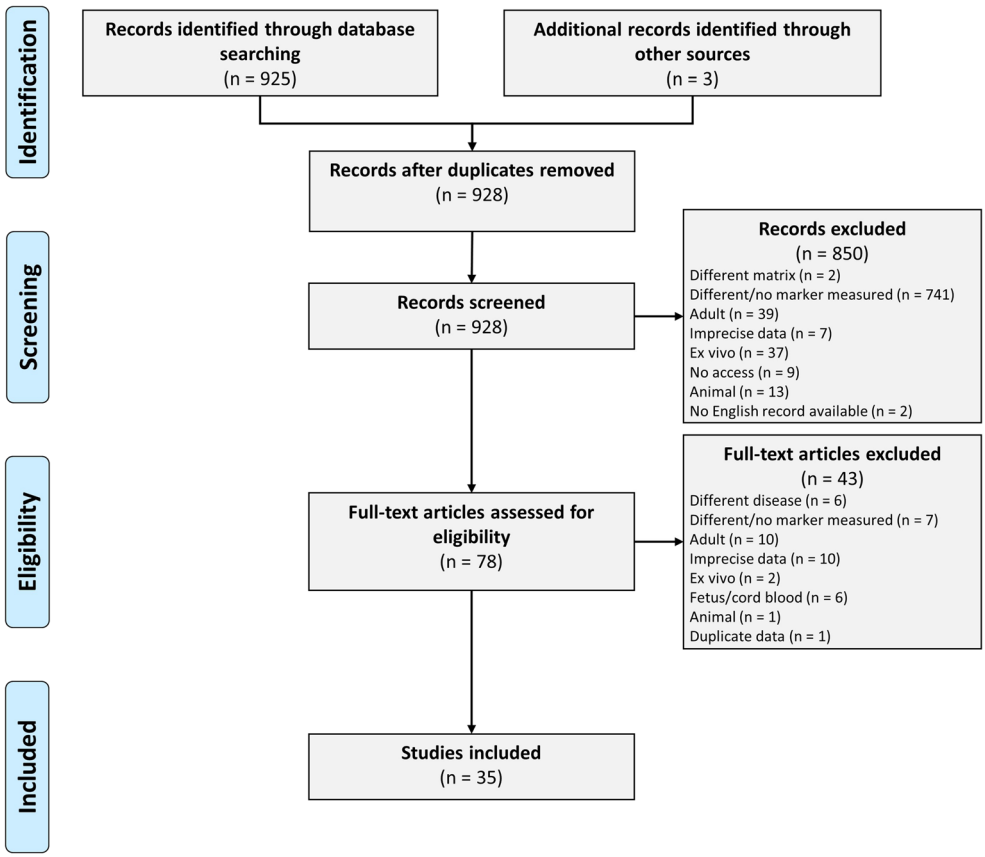

Fig. 1 Conducted search strategy expressed as PRISMA flow diagram

Overall, the mean and SD was 67.7 ± 7.1 pg/mL with a median of 50 and a wide range of 9.4–204 pg/mL, which is comparable with the further findings in this group [8].

An investigation of AngII levels in children with varying birthweights (1–7 days) indicated a sustained decrease in the strata of infants with normal birthweight (NBW) and moderate-low birthweight (MLBW) from birth (NBW, 74 pg/mL (range 3–443 pg/mL); MDLW, 43 pg/mL (range 5–438 pg/mL) (geometric mean (range))) to 7 days after birth (NBW, 19 pg/mL (range 1–127 pg/mL); MDLW, 8 pg/mL (range 5–254 pg/mL) (geometric mean (range))). In contrast, infants with a very low birthweight (VLBW) showed a marked increase in AngII concentrations of 34 pg/mL (range 5–201 pg/mL) to 76 pg/mL (range 7–1041 pg/mL) (geometric mean (range)) [7]. However, 2 years later, the same group noted a slight decline in AngII values from birth to day 35 in VLBW infants [9]. These contradicting findings in the newborn underline the lack of comprehensive knowledge in this age group (please refer to Table 1 and Fig. 2 for further results in the newborn population).

Infants and toddlers

The AngI plasma concentrations of 16 healthy infants (3–12 months) ranged from 94 to 244 pg/mL with a median of 157 pg/mL and thus tending to be lower than the obtained concentrations from newborns beforehand [6].

The obtained AngII values were equivalent to a range of 12–82 pg/mL and a median of 37 pg/mL [6]. A further cohort of 20 infants (1–12 months) exhibits comparable plasma concentrations of 33.6 ± 3.4 pg/mL (mean ± standard error (SE)) [13]. In contrast, Cruces et al. found higher levels in healthy infants with a median and interquartile range (IQR) of 10 (5–24) years of age, which amount to a median of 229 pg/mL with an IQR of 157–319 pg/mL. Moreover, 30 infants (30 days–10 months) showed AngII concentrations of 300 ± 30 pg/mL [11] and even 35 infants (1.5–13 months) a concentration of 1330 ± 1130 pg/mL [12]. These findings indicate the high variability which is not clearly clarified yet (please refer to Table 1 and Fig. 2 for further results regarding infants and toddlers).

Children and adolescents

The AngI values between a cohort of children with 1–4 years of age ($n = 10$) and a cohort of children with 4–8 years of age ($n = 9$) showed a decrease of plasma concentration from a median of 133 pg/mL (range 83–312 pg/mL) to a median of 99 pg/mL (range 63–183 pg/mL), respectively. The latter values did not notably differ to children with 8–13 years of age ($n = 10$) [6] but were higher than in a cohort of 32 children

Table 1 Angiotensin values, specifications, and analytics of investigated healthy population

Age	Statistical operator	*N*	AngI (pg/mL)	AngII (pg/mL)	Ang1–7 (pg/mL)	Statistical operator	Sampling procedure	Analytics	Collective	Reference
1–7 days	Range	16		Day 0: 34 (5–201) Day 7: 76 (7–1041)		Mean (range)	Day 0: at birth Day 7: supine	Plasma/ELISA	VLBW newborns 27.9 ± 2.9 weeks GA (mean ± SD)	Miyawaki et al. 2006 [7]
1–7 days	Range	16		Day 0: 43 (5–438) Day 7: 28 (5–254)		Mean (range)	Day 0: at birth Day 7: supine	Plasma/ELISA	MLBW newborns 33.8 ± 1.5 weeks GA (mean ± SD)	Miyawaki et al. 2006 [7]
1–7 days	Range	14		Day 0: 74 (3–443) Day 7: 19 (1–127)		Mean (range)	Day 0: at birth Day 7: supine	Plasma/ELISA	NBW newborns 38.9 ± 1.6 weeks GA (mean ± SD)	Miyawaki et al. 2006 [7]
1–11 days	Range	46		67.7 ± 7.1 (9.4–204)§		Mean ± SD (range)	Supine in the morning	Plasma + inhibitor/RIA	Newborn and infants with prematurity or jaundice	Pipkin et al. 1977 [8]
1–35 days	Range	9		Day 0: 55/day 7: 52 Day 21:52/day 35: 13		Mean	Supine in the morning	Plasma/ELISA	VLBW newborns and infants	Miyawaki et al. 2008 [9]
6 days	Mean	25		60.3 ± 9.2		Mean ± SD	n/a	Plasma/RIA	Newborns with prematurity or jaundice	Pipkin et al. 1975 [10]
1 week–3 months	Range	9	321 ± 112#	64 ± 31#		Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/RIA	Newborns, infants, and toddlers	Fiselier et al. 1983 [6]
30 days–10 months	Range	30		300 ± 30		Mean ± SD	n/a	Plasma/ELISA	Infants and toddlers	Tang et al. 2015 [11]
1.5–13 months	Range	35		1330 ± 1130		Mean ± SD	n/a	Plasma/ELISA	Infants and toddlers	Zaher et al. 2016 [12]
1–12 months	Range	20		33.6 ± 4.3		Mean ± SE	Recumbent in the afternoon	Plasma/RIA	Infants and toddlers	Van Acker et al. 1983 [13]
2 months–12 years	Range	63		37.8 ± 3.7 (5–103)		Mean ± SD (range)	Sober/supine in the morning	Plasma + inhibitor/RIA	Infants, toddlers, and children	Pipkin et al. 1981 [14]
3–12 months	Range	16	163 ± 49#	42 ± 21#		Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/RIA	Infants and toddlers	Fiselier et al. 1983 [6]
10 (5–24) months	Median (IQR)	60		229 (157–319)		Median (IQR)	n/a	Plasma/ELISA	Infants and toddlers with pneumonia	Cruces et al. 2012 [15]
1–4 years	Range	10	143 ± 69#	32 ± 23# ($n = 11$)		Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/RIA	Infants, toddlers, and children	Fiselier et al. 1983 [6]
1–13 years	Range	10		1780 ± 70		Mean ± SD	n/a	Plasma/ELISA	Infants, toddlers, and children	El-Deek et al. 2017 [16]
24.1 ± 8.6 months	Mean ± SD	30		29.5 ± 7.6§		Mean ± SD	n/a	Serum/ELISA	Infants and toddlers and children	Zhang et al. 2018 [17]
3.1–16.7 years	Range	32	26.4 ± 13.4	21.4 ± 8.7	16.2 ± 7.9	Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/RIA	Children and adolescents	Simões e Silva et al. 2004 [18]

Table 1 (continued)

Age	Statistical operator	*N*	AngI (pg/mL)	AngII (pg/mL)	Ang1–7 (pg/mL)	Statistical operator	Sampling procedure	Analytics	Collective	Reference
4–8 years	Range	9	103 ± 38#	24 ± 15#		Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/RIA	Children	Fiselier et al. 1983 [6]
5–12 years	Range	150		710 ± 530		Mean ± SD	Fasting	Serum/RIA	Children	Al-Daghri et al. 2010 [19]
6 and 9 years		2		39.9 ± 35.5#		Mean ± SD	Supine	Plasma/RIA	Male children	Tiosano et al. 2011 [20]
6–16 years	Range	33		11.5 (8.4–15.7)		Median (IQR)	Fasting	Plasma/RIA	Children and adolescents	Hjortdal et al. 2000 [21]
8–13 years	Range	31	♂: 77380 ± 35-570 ♀: 85280 ± 43-670	♂: 92340 ± 188-60 ♀: 82380 ± 231-40	♂: 31680 ± 24-260 ♀: 45750 ± 30-120	Mean ±SD	n/a	Plasma + inhibitor/HPLC-UV/-VIS	AGA birthweight children and adolescents	Franco et al. 2008 [22]
8–13 years	Range	35	♂: 79740 ± 42-980 ♀: 89110 ± 31-360	♂: 117810 ± 36-790 ♀: 86630 ± 296-00	♂: 41590 ± 31-150 ♀: 46160 ± 27-040	Mean ± SD	n/a	Plasma + inhibitor/HPLC-UV/-VIS	SGA birthweight children and adolescents	Franco et al. 2008 [22]
8–13 years	Range	10	105 ± 41#	24 ± 16#		Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/RIA	Children and adolescents	Fiselier et al. 1983 [6]
8.2 ± 0.5 years	Mean ± SD	9		13 ± 0.1#		Mean ± SE	Supine at 12.00 h	Plasma/RIA	Prepuberty boys	Mahler et al. 2015 [23]
8.3 ± 0.3 years	Mean ± SD	9		10.1 ± 1#		Mean ± SE	Supine at 12.00 h	Plasma/RIA	Prepuberty girls	Mahler et al. 2015 [23]
9.4 ± 2.6 years	Mean ± SD	131		570 (440–730)		Median (IQR)	Fasting	Serum/RIA	Children and adolescents	Al-Daghri et al. 2011 [24]
10.7 ± 0.9	Mean ± SD	10		15.4 ± 2.7#		Mean ± SD	Sitting in the morning	Plasma/RIA	Children and adolescents	Kamperis et al. 2008 [25]
10.0 ± 1 year	Mean ± SD	10		Girls: 107 ± 42		Mean ± SD	Supine in the night	Plasma/RIA	Female children	Mahler et al. 2012 [26]
11.1 ± 1.1 years	Mean ± SD	10		Boys: 71 ± 29		Mean ± SD	Supine in the night	Plasma/RIA	Male children and adolescents	Mahler et al. 2012 [26]
11.5 ± 0.6	Mean ± SD	11		12 ± 2.4#		Mean ± SD	Sitting in the morning	Plasma/RIA	Children and adolescents	Kamperis et al. 2012 [27]
11.9 ± 7.7 years	Mean ± SD	30		5.4 ± 0.9		Mean ± SD	n/a	Serum/ELISA	Children and adolescents	Gheissari et al. 2013 [28]
12–17 years	Range	4		99.0 ± 22.9#		Mean ± SD	Supine	Plasma/RIA	Female adolescents	Tiosano et al. 2011 [20]
12.8 ± 0.8 years	Mean ± SD	10		12.2 ± 2.1#		Mean ± SE	Supine at 12.00 h	Plasma/RIA	Puberty girls	Mahler et al. 2015 [23]
13.2 ± 0.8 years	Mean ± SD	10		Day: 10.4 ± 1.3 Night: 22.3 ± 3.1		Mean ± SE	Sitting at day supine at night	Plasma/RIA	Children and adolescents	Rittig et al. 2006 [29]
14 ± 0.9 years	Mean ± SD	10		14.8 ± 0.2#		Mean ± SE	Supine at 12.00 h	Plasma/RIA	Puberty boys	Mahler et al. 2015 [23]
14 years	Mean	50		22 (16.3–30.4)§	2.4 (1.3–6.3)§	Median (IQR)	Sitting	Plasma	Adolescents born preterm	South et al. 2017 [30]
14 years	Mean	70		23.3 (17.9–34.8)§	8.1 (2.3–13.2)§	Median (IQR)	Sitting	Plasma	Adolescents born preterm (ANCS)	South et al. 2017 [30]

Table 1 (continued)

Age	Statistical operator	*N*	AngI (pg/mL)	AngII (pg/mL)	Ang1–7 (pg/mL)	Statistical operator	Sampling procedure	Analytics	Collective	Reference
14 years	Mean	78		25 ± 13#	9 ± 10§	Mean ± SD	Sitting	Plasma + inhibitor/RIA	Adolescents/prematurely with VLBW/normotensive pregnancy	Washburn et al. 2015 [31]
14 years	Mean	49		23 ± 10#	8 ± 6§	Mean ± SD	Sitting	Plasma + inhibitor/RIA	Adolescents/prematurely with VLBW/preeclamptic pregnancy	Washburn et al. 2015 [31]

§Values calculated from pmol/L to pg/mL

Values generated via GetData Graph Digitizer 2.26.0.20, mean of three times conduct

n/a, data not available; *SD*, standard deviation; *IQR*, interquartile range; *VLBW*, very low birthweight; *MLBW*, moderate-low birthweight; *NBW*, normal birthweight; *GA*, gestational age; *RIA*, radioimmunoassay; *ELISA*, enzyme-linked immunosorbent assay; *HPLC*, high-performance liquid chromatography; *UV/VIS*, ultraviolet/visible spectroscopy; *AGA*, appropriate for gestational age; *SGA*, small for gestational age; *ANCS*, antenatal corticosteroids

and adolescents (3.1–16.7 years) with 26.4 ± 13.4 pg/mL [18]. In opposition, remarkable higher concentrations were observed in 8–13-year-old boys and girls with appropriate gestational birthweight (AGA) and small gestational birthweight (SGA). Obtained values regarding AGA boys and girls were 77.4 ± 35.6 ng/mL and 85.3 ± 43.7 ng/mL, respectively, whereas values obtained from SGA boys and girls amount to 79.7 ± 43.0 ng/mL and 89.1 ± 31.4 ng/mL, correspondingly [22].

AngII values measured by the same group showed slightly higher concentration ranges. The mean plasma concentrations of boys and girls in the SGA and AGA groups varied between 82.4 ng/mL and 117.8 ng/mL [22] compared with children ($n = 10$) with the same age being born with NBW (median 22 pg/mL (range 12–67 pg/mL)) [6]. Several publications reported similar lower pg/mL levels of circulating AngII levels in children and adolescents, supported by relatively large numbers of participants, with a broad range of age for included paediatrics [6, 17, 18, 20, 21, 25–31]. Apart from that, higher concentrations were found in 1–13-year-old subjects ($n = 10$) with 1780 ± 70 pg/mL [16], as well as in 5–12 years ($n = 150$) and 9.4 ± 2.6-year (mean ± SD)-old children ($n = 131$) showing serum levels of 710 ± 530 pg/mL and a median of 570 pg/mL (IQR 440–730 pg/mL), respectively [19, 24].

Ang1–7 plasma levels were reported in children and adolescents only. Concentrations of 16.2 ± 7.9 pg/mL were found in 3.1–16.7-year-old subjects ($n = 32$) by Simões e Silva et al. in 2004. In adolescents (14 years) born preterm without ($n = 50$) and with antenatal corticosteroids ($n = 70$), low levels of Ang1–7 with a median of 2.4 pg/mL (IQR 1.3–6.3 pg/mL) versus 8.1 pg/mL (IQR 2.3–13.2 pg/mL) were observed [30]. Measured Ang1–7 levels of adolescents (14 years) born prematurely with VLBW under normotensive ($n = 78$) or preeclamptic ($n = 49$) pregnancy were 9 ± 10 pg/mL and 8 ± 6 pg/mL, respectively. Comparable with the previously reported AngI and AngII values, remarkable high concentrations occurring in AGA and SGA children amount to more than 31.7 ng/mL (mean) [22] (please refer to Table 1 and Fig. 2 for further results in the population of children and adolescents).

Sex-related differences

Sex hormones are believed to play a role in the regulation of the adult RAAS, which is reflected in altered blood pressure and pathogenesis of cardiovascular and renal diseases [32]. Whereas most of the reported studies in this review included a balanced number of male and female participants, sex-related deviations in paediatric population regarding angiotensin peptides were reported infrequently. However, based on the growing interest in personalised medicine approaches,

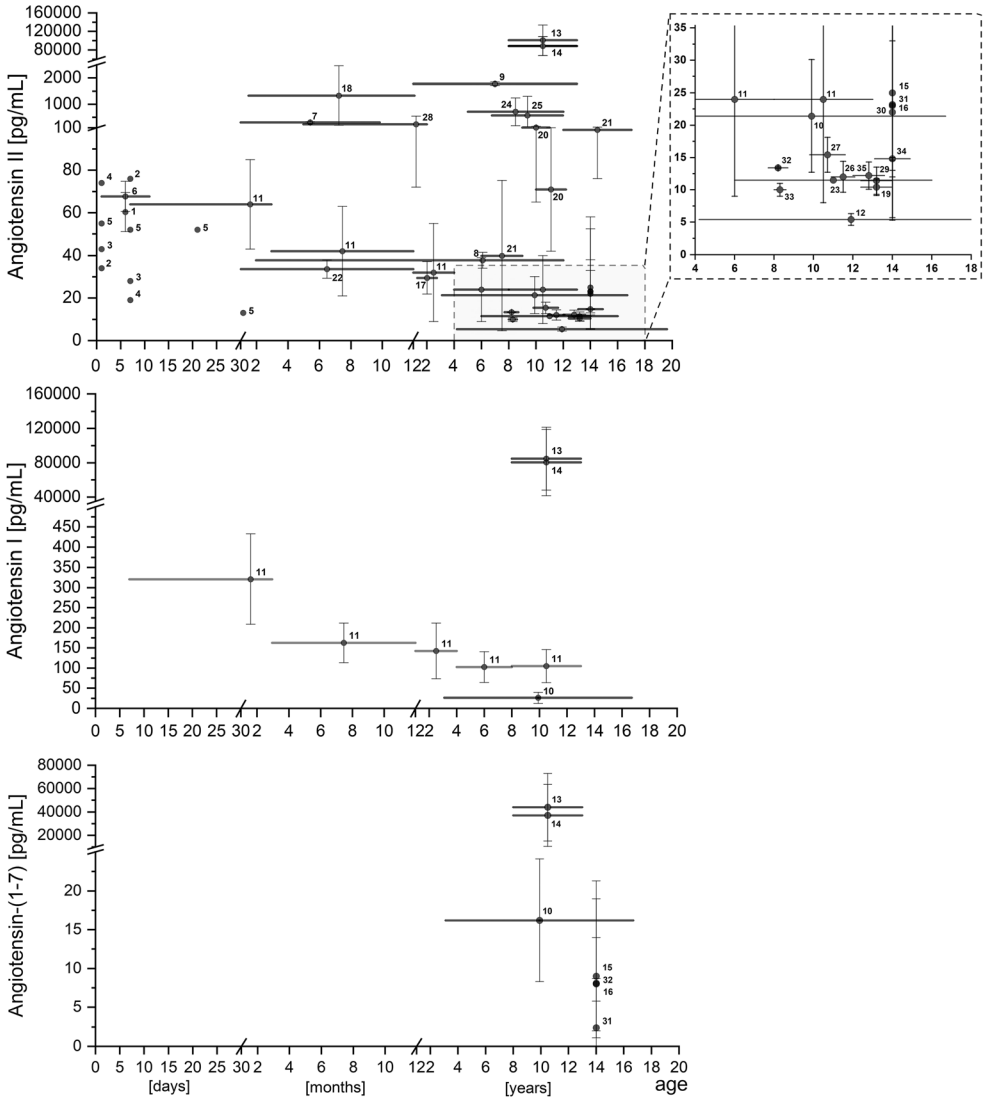

Fig. 2 Age-related change of AngI, AngII, and Ang1–7 levels in healthy population during childhood. Angiotensin concentrations are expressed as mean ± standard deviation (SD), unless otherwise classified; thick horizontal line: range of age of investigated population, unless otherwise classified; SE: standard error; IQR: interquartile range; (1) Pipkin et al. 1975 ($n = 25$); (2) Miyawaki et al. 2006 (very low birthweight, $n = 16$); (3) Miyawaki et al. 2006 (moderate-low birthweight, $n = 16$); (4) Miyawaki et al. 2006 (normal birthweight, $n = 16$); (5) Miyawaki et al. 2008 (very low birthweight, $n = 9$); (6) Pipkin et al. 1977 ($n = 46$); (7) Tang et al. 2015 ($n = 30$); (8) Pipkin et al. 1981 ($n = 63$); (9) El-Deek et al. 2017 ($n = 10$); (10) Simões e Silva et al. 2004 ($n = 32$); (11) Fiselier et al. 1983 ($n = 9$–16); (12) Gheissari et al. 2013 (age as mean ± SD) ($n = 30$); (13) Franco et al. 2008 (appropriate for gestational age) ($n = 31$); (14) Franco et al. 2008 (small for gestational age) ($n = 35$); (15) Washburn et al. 2015 (very low birthweight + normotensive pregnancy, $n = 78$); (16) Washburn et al. 2015 (very low birthweight + preeclamptic pregnancy, $n = 49$); (17) Zhang et al. 2018 (age as mean ± SD) ($n = 30$); (18) Zaher et al. 2015 ($n = 35$); (19) Rittig et al. 2006 (concentration and age as mean ± SE) ($n = 10$); (20) Mahler et al. 2012 (age as mean ± SD) ($n = 10$); (21) Tiosano et al. 2001 ($n = 2$–4); (22) Van Acker et al. 1983 ($n = 20$); (23) Hjortdal et al. 2000 (concentration as median (IQR), $n = 33$); (24) Al-Daghri et al. 2010 ($n = 150$); (25) Al-Daghri et al. 2011 (concentration as median (IQR), age as mean ± SD, $n = 131$); (26) Kamperis et al. 2012 (age as mean ± SD, $n = 11$); (27) Kamperis et al. 2008 (age as mean ± SD, $n = 10$); (28) Cruces et al. 2012 (concentration and age as median (IQR), $n = 60$); (29) Rittig et al. 2010 (age as mean ± SD, $n = 10$); (30) South et al. 2017 (concentration as median (IQR), $n = 50$); (31) South et al. 2017 (antenatal corticosteroids, concentration as median (IQR), $n = 70$); (32) Mahler et al. 2015 (prepuberty boys, concentration as mean ± SE, $n = 9$); (33) Mahler et al. 2015 (prepuberty girls, concentration as mean ± SE, $n = 9$); (34) Mahler et al. 2015 (puberty boys, concentration as mean ± SE, $n = 10$); (35) Mahler et al. 2015 (puberty girls, concentration as mean ± SE, $n = 10$)

gender could play an increasingly important role in prospective therapy of CVD and RF [33].

AngI and AngII values of 32 boys and 23 girls were obtained for children subdivided into groups of 1 week–3 months, 3 months–1 year, 1–4 years, 4–8 years, and 8–13 years. No significant differences ($p > 0.05$) of plasma concentrations were found between males and females in the corresponding groups [6].

In contrast, findings of Pipkin et al., including 20 boys and 43 girls (2 months–12 years), showed evidence ($p < 0.02$) of

higher AngII plasma concentrations (34.7 ± 4.5 pg/mL) in girls versus (24.9 ± 5.5 pg/mL) in boys. Subdividing into roughly numerical-equal groups of younger than 8 and older than 8 years of age showed significant ($p < 0.01$) lower AngII values in boys under 8 years of age. For boys older than 8 years, an equal (but not significant ($p > 0.6$)) trend could be observed [14].

A further study was able to gather gender-specific data on AngI, AngII, and Ang1–7 in 66 children (8–13 years). However, no significant, sex-related variations (considering the high intergroup SD) could be ascertained for all RAAS peptides between AGA boys (AngI, 77.4 ± 35.6 ng/mL; AngII, 92.3 ± 18.9 ng/mL; Ang1–7, 31.7 ± 24.3 ng/mL) and girls (AngI, 85.3 ± 43.7 ng/mL; AngII, 82.4 ± 23.1 ng/mL; Ang1–7, 45.8 ± 30.1 ng/mL) as well as between SGA boys (AngI, 79.7 ± 43.0 ng/mL; AngII, 117.8 ± 36.8 ng/mL; Ang1–7, 41.6 ± 31.2 ng/mL) and girls (AngI, 89.1 ± 31.4 ng/mL; AngII, 86.6 ± 29.6 ng/mL; Ang1–7, 46.2 ± 27.0 ng/mL) [22].

In a similar subject, Washburn et al. investigated AngII and Ang1–7 values in VLBW infants of 14 years of age, which were born prematurity, either in normotensive or preeclampsia conditions. AngII and Ang1–7 values of normotensive male children were 19 ± 10 pg/mL and 9 ± 13 pg/mL, compared with normotensive female children of 29 ± 13 pg/mL and 9 ± 8 pg/mL, respectively. The preeclampsia-born male children showed AngI and Ang1–7 values of 22 ± 9 pg/mL and 10 ± 9 pg/mL versus 24 ± 10 pg/mL and 7 ± 4 pg/mL, respectively, for female preeclampsia-born children [31]. Overall, no significant differences could be observed in circulating peptide concentrations between both genders. Further, AngII values were obtained as part of a study including 73 boys (9.0 ± 1.8 years (mean ± SD)) and 77 girls (9.3 ± 2 years (mean ± SD)). Serum concentrations for boys were 650 ± 300 pg/mL, while values in girls were slightly higher (730 ± 600 pg/mL) but did not reach statistical significance ($p = 0.45$) [19]. Supplementary evidence for similar, gender-independent levels of AngII in paediatric population was obtained by Mahler et al. No significant sex-related differences in baseline concentrations could be observed in prepuberty boys (13.4 ± 0.1 pg/mL (mean ± SE), 8.2 ± 0.5 years, $n = 9$) and girls (10.1 ± pg/mL (mean ± SE), 8.3 ± 0.3 years, $n = 9$) versus puberty boys (14.8 ± 0.2 pg/mL (mean ± SE), 14.0 ± 0.9 years, $n = 10$) and girls (12.2 ± 2.1 pg/mL (mean ± SE), 12.8 ± 0.8 years, $n = 10$) ($p = 0.879$) [23]. In contrast, the same group measured significant ($p = 0.03$) different night time levels of AngII in boys (71 ± 29 pg/mL (mean ± SE), 10.6 ± 1.2 years, $n = 10$) and girls (107 ± 42 pg/mL (mean ± SE), 10.6 ± 1.2 years, $n = 10$) [26].

Pharmacological intervention in diseased children

Children ($n = 32$) at 10.4 ± 4.8 years (mean ± SD) with hypertensive chronic renal failure (CRF) receiving antihypertensive medications showed an elevation as compared with normotensive CRF children (12 ± 4 years (mean ± SD), $n = 28$) without antihypertensive medication for plasma levels of AngI (171.8 ± 85.4 pg/mL versus 26.7 ± 6.7 pg/mL), Ang1–7 (140.8 ± 58 pg/mL versus 18.6 ± 6.8 pg/mL), and AngII (84.2 ± 52.9 pg/mL versus 22.4 ± 9.1 pg/mL). In addition, a similar proportion was observed with respect to 11.2 ± 4-year-old (mean ± SD) healthy controls ($n = 32$) [34]. For patients in the same collective receiving antihypertensive medication either with ($n = 20$) or without angiotensin-converting enzyme inhibitors (ACEi) ($n = 14$), a significant elevation for AngI (199.0 ± 47.6 pg/mL versus 135.3 ± 44.6 pg/mL) and Ang1–7 (159.1 ± 62.6 pg/mL versus 114.7 ± 39.7 pg/mL), as well as significantly lower levels for AngII (53.6 ± 32.5 pg/mL versus 127.9 ± 45.6 pg/mL), could be observed. Additionally, antihypertensive medication led to a significant elevation of peptide levels in a hypertensive end-stage renal disease (ERSD) ($n = 18$) group compared with ESRD patients without antihypertensive medication ($n = 3$) for AngI (349 ± 33.1 pg/mL versus 230.4 ± 47.6 pg/mL) and Ang1–7 (443.8 ± 58.5 pg/mL versus 271.4 ± 32.9 pg/mL). Yet, AngII concentration did not raise significantly (117.2 ± 25.6 pg/mL versus 89.3 ± 9.7 pg/mL) [34].

In contrast, antihypertensive-treated ERSD children with additional ACEi ($n = 12$) and without additional ACEi ($n = 9$) showed comparable results for AngI, Ang1–7, and AngII [34]. Moreover, treatment of 11.6 ± 4.8-year-old (mean ± SD) children suffering from essential hypertension with CCB alone ($n = 12$) or non-pharmacological treatment ($n = 3$) showed no differences in RAAS profile before and after treatment for AngI (36.5 ± 11.4 pg/mL versus 35.7 ± 11.2 pg/mL), Ang1–7 (78.5 ± 20.4 pg/mL versus 79.8 ± 23.4 pg/mL), and AngII (21.8 ± 10.6 pg/mL versus 22.5 ± 10.9 pg/mL) [18].

Moreover, administration of fosinopril in addition to prednisone in the context of a randomised controlled trial in 8.7 ± 3.5-year-old (mean ± SD) children ($n = 25$) with steroid-resistant idiopathic nephrotic syndrome (SRINS) revealed no significant difference of AngII values as compared with 8.7 ± 3.7-year-old (mean ± SD) SRINS children receiving prednisone alone ($n = 20$) after 12 weeks of treatment (78.9 ± 26.2 pg/mL versus 79.0 ± 35.8 pg/mL) [35] (for further results regarding pharmacological interventions, please refer to Table 2 and Fig. 3).

Mechanical intervention in diseased children

The impact on circulating AngII concentrations of newborns and infants before and after bidirectional Glenn (BDG) procedure (13 ± 5 months (mean ± SE), $n = 15$), Fontan procedure (36 ± 10 months (mean ± SE), $n = 18$), or elective ventricular septal defect (VSD) repair (25 ± 8 months (mean ± SE), $n = 10$) during catheterisation was investigated by Mainwaring et al. AngII levels were slightly elevated in the BDG group

Table 2 Angiotensin values, specifications, and analytics of investigated cardiovascular- and renal-diseased population

Age	Statistical operator	*N*	AngI (pg/mL)	AngII (pg/mL)	Ang1–7 (pg/mL)	Statistical operator	Sampling procedure	Analytics	Collective	Reference
4 months	Single value	1		622		Single value	n/a	Plasma/RIA	A female infant with Bartter's syndrome	Nakagawa et al. 1997 [36]
1 year up to 16 years	Single value	1	No treatment: 3875 2.4 years of treatment: 541 15 years of treatment: 536	No treatment: 860 2.4 years of treatment: 85 15 years of treatment: 151		Single value	n/a	Plasma/RIA	A female child with Bartter's syndrome treated with indomethacin	Nakagawa et al. 1997 [36]
13 ± 5 months	Mean ± SE	15		33 ± 4		Mean ± SE	n/a	Plasma/RIA	Infants and toddlers (before) undergoing BDG procedure	Mainwaring et al. 1994 [37]
1.6 ± 1 years	Mean ± SD	29		199 ± 223		Mean ± SD	During cardiac catheterisation	n/a	Hypoplastic left heart syndrome infants, toddlers, and children undergoing Norwood procedure	Saiki et al. 2016 [38]
1.3 ± 2.8 years	Mean ± SD	27		38 ± 55		Mean ± SD	During cardiac catheterisation	n/a	Infants, toddlers, and children suffering from pulmonary atresia with AP shunt	Saiki et al. 2016 [38]
25 ± 8 months	Mean ± SE	10		31 ± 2		Mean ± SE	n/a	Plasma/RIA	Infants, toddlers, and children with VSD	Mainwaring et al. 1994 [37]
36 ± 10 months	Mean ± SE	18		40 ± 3		Mean ± SE	n/a	Plasma/RIA	Children (before) undergoing Fontan procedure	Mainwaring et al. 1994 [37]
2.2–17.9 years	Range	23	26.7 ± 6.7	22.4 ± 9.1	18.6 ± 6.8	Mean ± SD	Sober/supine in the morning	Plasma + inhibitor/-RIA	Normotensive children and adolescents with CRF	Simões e Silva et al. 2006 [34]
2.2–17.2 years	Range	34	171.8 ± 85.4*	84.2 ± 52.9*	140.8 ± 58.0*	Mean ± SD	Sober/supine in the morning before medication	Plasma + inhibitor/-RIA	Hypertensive children and adolescents with CRF	Simões e Silva et al. 2006 [34]
2.2–15.5 years	Range	12	81.4 ± 24.8*	59.3 ± 17.0*	41.0 ± 10.5*	Mean ± SD	Supine in the morning untreated	Plasma + inhibitor/-RIA	Children and adolescents with renovascular hypertension	Simões e Silva et al. 2004 [18]
2.7–17.7 years	Range	12	Untreated: 36.5 ± 11.-4 Treated: 35.7 ± 11.-2	Untreated: 21.8 ± 10.-6 Treated: 22.5 ± 10.-9	Untreated: 78.5 ± 20.-4* Treated: 79.8 ± 23.-4*	Mean ± SD	Supine in the morning	Plasma + inhibitor/-RIA	Children and adolescents with essential hypertension	Simões e Silva et al. 2004 [18]
5.8 ± 3.6 years	Mean ± SD	30		13 ± 7		Mean ± SD	During cardiac catheterisation	n/a	Children with VSD or repaired VSD/ASD	Saiki et al. 2016 [38]
5.9–16.8 years	Range	21	332.1 ± 54.5*	113.2 ± 25.8*	419.2 ± 82.2*	Mean ± SD	Supine in the morning	Plasma + inhibitor/-RIA	Children and adolescents with ESRD	Simões e Silva et al. 2006 [34]
6–18 years	Range	8		42 (15–102)		Median (IQR)	During cardiac catheterisation	Plasma/RIA	Children and adolescents underwent BDG with pulmonary atresia, pulmonary stenosis, tricuspid atresia, or transposition of the great arteries	Hjortdal et al. 2000 [21]
8.7 ± 3.5 years	Mean ± SD	25		78.9 ± 26.2		Mean ± SD	In the morning after 12 weeks of treatment	Serum/RIA	Normotensive children and adolescents with SRINS receiving prednisone + fosinopril	YI et al. 2006 [35]
8.7 ± 3.7 years		20		79.0 ± 35.8		Mean ± SD		Serum/RIA		YI et al. 2006 [35]

Table 2 (continued)

Age	Statistical operator	*N*	AngI (pg/mL)	AngII (pg/mL)	Ang1–7 (pg/mL)	Statistical operator	Sampling procedure	Analytics	Collective	Reference
	Mean ± SD						In the morning. After 12 weeks of treatment		Normotensive children and adolescents with SRINS receiving prednisone	
10 years		1	Inferior vena cava: 990 Right ventricle: 1200	Inferior vena cava: 16 Right ventricle: 10		Single value	n/a	n/a	A female child with pulmonary hypertension and extrahepatic portal hypertension	Tokiwa et al. 1992 [39]
10.4 ± 4.6	Mean ± SD	6	Before medication: 80–2100 With medication: 390–5370	Before medication: 53–3530 With medication: 0–700		Range	Supine in the morning before/after captopril administration	n/a	Children and adolescents with severe hypertension and diverse renal diseases	Friedman et al. 1980 [40]
12.4 ± 5.3 years	Mean ± SD	6		30.16 ± 15.81		Mean ± SD	Before haemodialysis	Serum + EDTA/RIA	Anephric hypertensive adolescents receiving haemodialysis	Seguias et al. 2001 [41]
13.8 ± 3.7 years	Mean ± SD	6		35.8 ± 10.5		Mean ± SD	Before haemodialysis	Serum + EDTA/RIA	Anephric normotensive adolescents receiving haemodialysis	Seguias et al. 2001 [41]
14.7 ± 3.4 years	Mean ± SD	30		7.4 ± 0.7*		Mean ± SD	n/a	Serum/ELISA	Adolescent kidney transplant recipients	Gheissari et al. 2013 [28]
15 ± 0.4 years	Mean ± SD	18		Supine position: 27.7 ± 3# After 15 min of HUT test: 38.1 ± 4.2-#	Supine position: 12.9 ± 1.8-# After 15 min of HUT test: 15.8 ± 1.7-#	Mean ± SD	Supine during HUT test	RIA	Adolescents with symptoms for orthostatic intolerance with normal HUT test	Wagoner et al. 2016 [42]
15 ± 0.4 years	Mean ± SD	30		Supine position: 30 ± 2.2# After 15 min of HUT test: 48.6 ± 3.6-#	Supine position: 14.9 ± 1.1-# After 15 min of HUT test: 16.5 ± 1.6-#	Mean ± SD	Supine during HUT test	RIA	Adolescents with symptoms for orthostatic intolerance with abnormal HUT test	Wagoner et al. 2016 [42]

*Significant higher values compared with healthy control group

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n/a, data not available; *SD*, standard deviation; *IQR*, interquartile range; *SE*, standard error; *RIA*, radioimmunoassay; *ELISA*, enzyme-linked immunosorbent assay; *BDG*, bidirectional Glenn; *ASD*, atrial septal defect; *VSD*, ventricular septal defect; *CRF*, chronic renal failure; *ESRD*, end-stage renal disease; *HUT*, head-up tilt

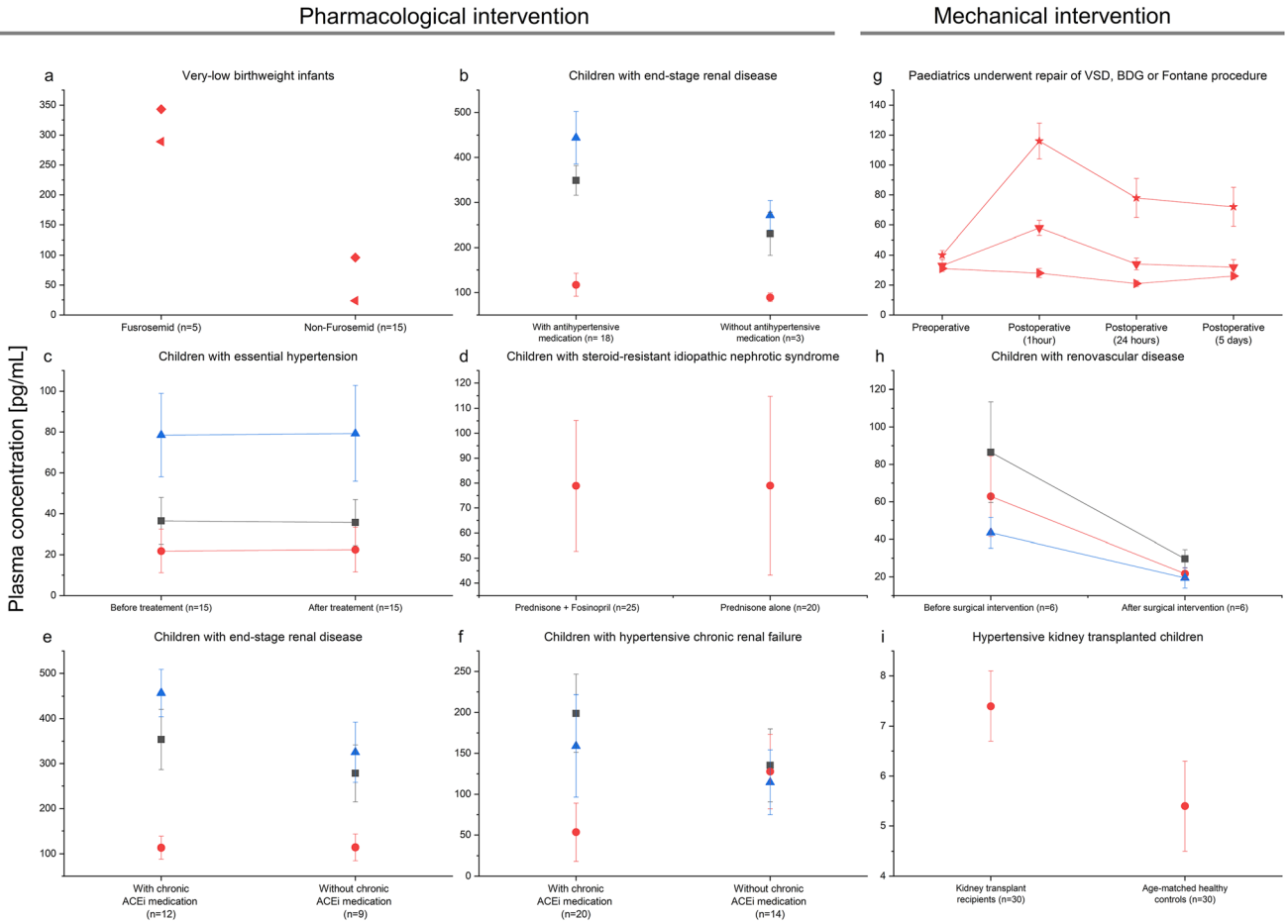

Fig. 3 Intervention-related changes of peptide concentrations expressed as mean ± SD (if not otherwise classified); lines between symbols: identical patients before and after intervention; VSD: ventricular septal defect; BDG: bidirectional Glenn; CCB: calcium channel blocker; ACEi: angiotensin-converting enzyme inhibitor; ESRD: end-stage renal disease; ■: AngI; ●: AngII; ▲: Ang1–7. **a** AngII values in very low birthweight children. ◆: AngII values 21 days after birth; ◀: AngII values 35 days after birth [9]. **b** Children with ESRD treated with CCB + ACEi ($n = 12$), CCB + loop-diuretic ($n = 2$), CCB ($n = 4$), or untreated ($n = 3$) [34]. **c** Children with essential hypertension treated with CCB ($n = 12$) or non-pharmacological ($n = 3$) [18]. **d** Normotensive children with steroid-resistant idiopathic nephrotic syndrome receiving prednisone + fosinopril ($n = 25$) or prednisone alone ($n = 20$) [35]. **e** Children with ESRD receiving ACEi ($n = 12$) or no ACEi ($n = 9$) [34]. **f** Children with hypertensive chronic renal failure receiving ACEi ($n = 20$) or no ACEi ($n = 14$). [34]. **g** AngII values (mean ± SE) of paediatrics underwent cardiac surgeries. ▶: AngII values in infants and toddlers (age 25 ± 8 months, $n = 10$) underwent repair of VSD; ▼: AngII values in infants and toddlers (age 13 ± 5 months, $n = 15$) underwent BDG procedure; ★: AngII values in children (age 36 ± 10 months, $n = 8$) underwent Fontan procedure [37]. **h** Children with renovascular disease before and after renal angioplasty ($n = 5$) or nephrectomy ($n = 1$) [18]. **i** Hypertensive kidney-transplanted children ($n = 30$) and age-matched healthy controls ($n = 30$) [41]

at 1 h after operation (58 ± 5 pg/mL (mean ± SE)), compared with the preoperative measurements (58 ± 5 pg/mL (mean ± SE)), but returned to their preoperative values after 24 h (34 ± 4 pg/mL (mean ± SE)) and stayed constant until day 5 after operation (32 ± 5 pg/mL (mean ± SE)). Preoperative AngII values in the Fontan group were 40 ± 3 pg/mL (mean ± SE) and increased significantly 1 h after operation (116 ± 12 pg/mL (mean ± SE)), followed by a decrease in 24 h (78 ± 13 pg/mL (mean ± SE)) and 5 days (72 ± 13 pg/mL (mean ± SE)) but remained at significant elevated levels [37].

In a different manner, renal surgical correction (renal angioplasty ($n = 5$), nephrectomy ($n = 1$)) in 6 children with renovascular hypertension led to a significant decrease in plasma concentrations of peptide levels from before (AngI, 86.5 ± 26.9 pg/mL; Ang1–7, 43.5 ± 8.2 pg/mL; AngII, 62.9 ± 21.5 pg/mL) to 6 months after successful surgery (AngI, 29.7 ± 4.8 pg/mL; Ang1–7, 19.5 ± 5.5 pg/mL; AngII, 21.8 ± 2.9 pg/mL) (for further results regarding mechanical interventions, please refer to Table 2 and Fig. 3).

Discussion

In the healthy paediatric population, AngI values were higher than AngII values, yet both plasma concentrations decreased constantly during early childhood and stayed constant afterwards, showing still higher values than in adults [4, 6]. In the case of Ang1–7, data in paediatrics is insufficiently available

to generate a reliable statement, although the obtained levels appear to be low in the paediatric RAAS if compared with adults [4].

Whereas all values were obtained from healthy controls, the variation of determined values is high between each study. The phenomenon may possibly be explained by different races, the impact of sampling, used inhibitor-cocktails, matrix, sample processing procedures, and analytical principals of measurement (e.g. RIA, ELISA, or UV/VIS). Moreover, AngIII and AngIV, as well as recently investigated bioactive peptides of the RAAS like angioprotectin and angiotensin A, could be subject to misinterpretation of angiotensin concentrations due to the missing selectivity of applied immunoassays [43, 44]. Thus, the implications on the paediatric RAAS due to AngIII and AngIV besides further bioactive RAAS peptides (e.g. angioprotectin, angiotensin A, and alamandine) are still insufficiently investigated. Consequently, an overestimation of AngII and Ang1–7 impact on the RAAS in paediatric subjects is conceivable.

In contrast to gender-specific variations of the RAAS in adults [32, 45], no clear evidence for differences between male and female infants and children regarding circulating AngI, AngII, and Ang1–7 concentrations in paediatric population could be demonstrated. Hence, sex hormones which are believed to play a regulatory role in the adult RAAS [45] seem to be less distinctive for a discriminatory effect in children, suggesting that the gender-specific influence of the RAAS will be settled after childhood.

RAAS profiles could be subject to different states of hypertension and renal diseases [23, 46]. Because of conflicting evidence for the alteration of concentrations of RAAS components during and after treatment of cardiovascular- and renal-diseased children, evaluation of pharmacological and mechanical treatment effects in the very youngest is mandatory for a better prediction of therapeutic effects in the future. However, consistent evidence for changes of the angiotensin peptides related to antihypertensive drugs and surgical interventions in children is still discussed. Pharmacological interventions indicate to have an impact on circulating peptide concentrations due to the influence of antihypertensive medication which interferes with renal processes (especially ACEi), yet the evidence is still conflicting. However, a normalisation of angiotensin peptides caused by surgical intervention is anticipated (Fig. 4).

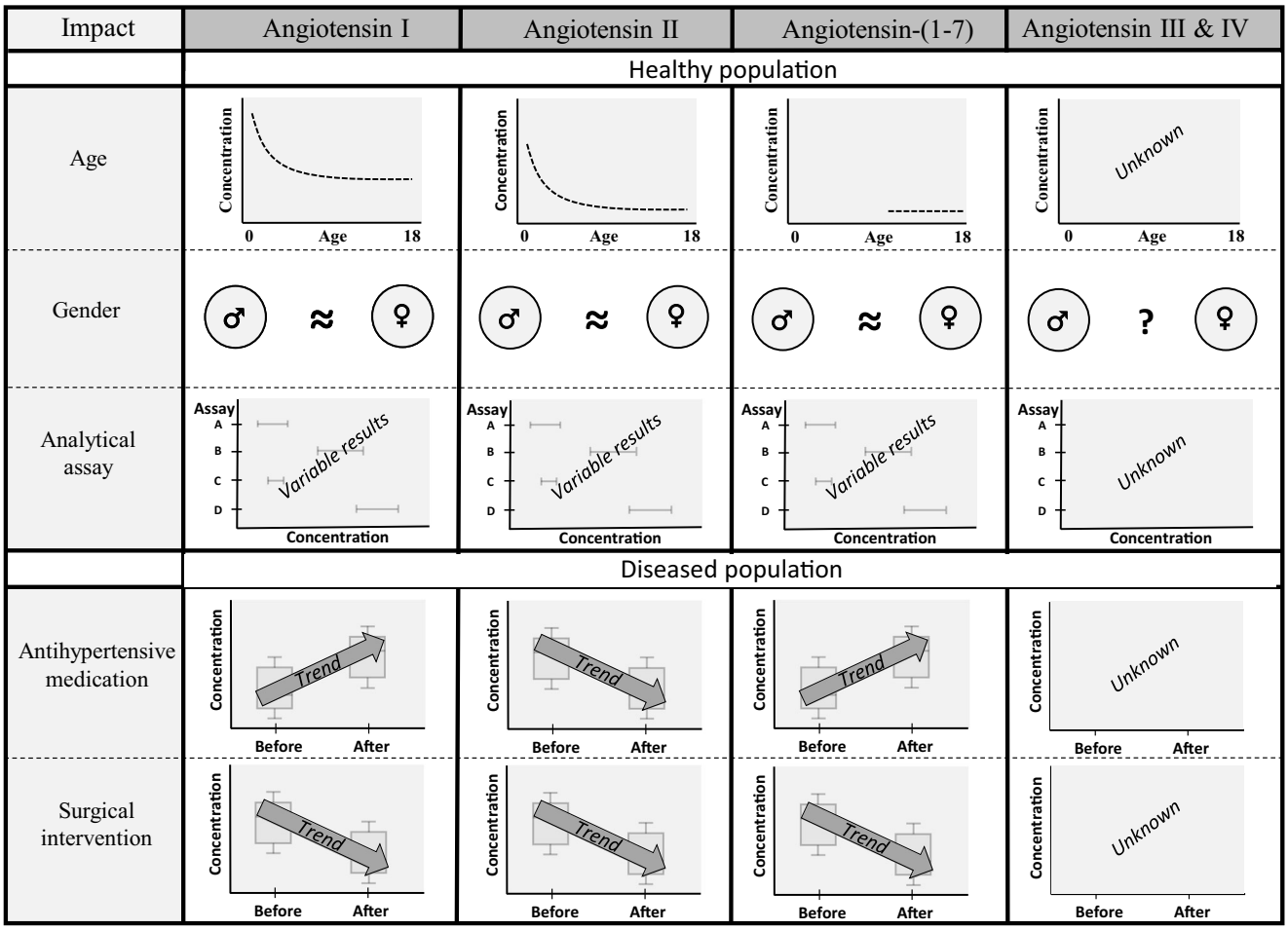

Fig. 4 Impact of examined factors on plasma and serum concentrations of angiotensin peptides in paediatric population

The review provides a reliable compilation of angiotensin concentrations during childhood as well as identification of cardiac and renal influences. Since drugs in paediatric care are still prevalently used off-label [47], several initiatives like the European Commission aim to counteract the safety risks resulting from off-label use by increased funding of paediatric studies (e.g. the seventh framework program "Labeling of enalapril in neonates up to adolescents" trial). However, the direct comparison between control groups and severely diseased children is often limited due to ethical constraints regarding the inclusion of healthy children in clinical trials. Diligently compiled pharmacodynamic data from literature might support a meaningful assessment of obtained study results in an overall context and serve as supportive reference for paediatric RAAS for this kind of trial.

Limitations

This review includes only MEDLINE database–listed publications that were available in the English language (language bias). In addition, inclusion criteria not mentioned in the title or abstract could potentially be missed out. Incomplete reported data (e.g. unspecific age, concentration units, assays, health status of participants) was excluded, leading to a more particularised dataset.

While blood sampling of entirely healthy children is ethically questionable, some of the reported values of healthy children were obtained during routine investigation or hospitalisation caused by various diseases. It was anticipated that these impacts are not to be RAAS-related. However, the influence of the plasma concentration cannot be completely ruled out.

Conclusion

Age has a major impact on circulating AngI, AngII, and Ang1–7, especially in the newborn period with decreasing values from newborns to adolescents. Nevertheless, gender did not impact plasma concentrations of angiotensin peptides in paediatrics. Cardiac- and renal-diseased children show generally higher concentrations than healthy controls; nonetheless, data for diseased newborns and infants is lacking. Changes in paediatric population due to antihypertensive treatment could be indicated, but not evidently proven, whereas evidence for alterations in angiotensin peptides caused by cardiac and renal surgery exists.

To provide a comprehensive picture of the paediatric RAAS, deeper analysis of the RAAS including novel peptides like AngIII and AngIV, which were not investigated in paediatrics yet, is a rational approach to gain reliable data for a better understanding of the maturing RAAS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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