Journal of Cardiology 74 (2019) 388–393

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Inferior vena cava, abdominal aorta, and IVC-to-aorta ratio in healthy Caucasian children: Ultrasound *Z*-scores according to BSA and age

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ARTICLE INFO

Article history:
Received 10 October 2018
Received in revised form 11 January 2019
Accepted 28 February 2019
Available online 2 April 2019

Keywords:
Pediatric ultrasound
Inferior vena cava
Aorta
Collapsibility index
Reference value

ABSTRACT

The pediatric ultrasound measurement of the inferior vena cava (IVC) and aorta (AO) with the study of the collapsibility index (CI) and of IVC-to-AO ratio (IVC/AO) can provide clinicians in the acute care setting with information on abnormal volume status but one of the major limitations is a lack of reference normal values by body surface area (BSA) and age. The aim of this study was to provide reference ranges for the sonographic measurement of IVC, AO, and IVC/AO ratio in healthy Caucasian Italian children.

Methods: We enrolled prospectively 516 healthy Caucasian Italian children aged between 1 month and 16 years. Echocardiographic IVC and AO diameters were collected and presented separately for children aged ≤1 year and for children aged over 1 year. For children >1 year we categorized subjects into 3 years classes. CI and IVC/AO for the systolic aortic diameter were then calculated. For children over 1 year, age reference ranges were age-related or BSA-related; for children of ≤1 year, reference ranges were determined with their 90% confidence intervals regardless of age and of BSA.

Results: Tables and charts with reference ranges for all the echocardiographic measurements are presented for children aged >1 year according to age and BSA. The equations to obtain percentile and *Z*-score for each echocardiographic measurement are provided. The reference ranges for children aged ≤1 year are shown considering the small 90% confidence intervals for upper and lower limits.

CI was 30% (SD 17%) in children >1 year and 36% (SD 16%) in children <1 year. IVC/AOs showed age-dependent values from 0.83 (SD 0.20) age <1 year to 1.22 (SD 0.31) in older subjects.

Conclusions: We report reliable reference ranges for echocardiographic measurement of IVC, AO, CI, and IVC/AO for a Caucasian Italian healthy pediatric population.

Background

The optimizing of the intravascular volume status is an essential aim in the emergency room to estimate volume repletion or fluid overload both in adults and children. Early detection and correction of hypovolemia may limit and/or reverse tissue hypoxia and improve patient outcome whereas an inappropriate fluid administration may precipitate heart failure [1]. No individual clinical sign, symptom, or laboratory test has demonstrated adequate sensitivity and specificity mainly in children [2]. The point of care ultrasound can provide a rapid and non-invasive diagnostic tool for the assessment of intravascular volume. Previous studies in adult patients showed a correlation between inferior vena cava (IVC) diameter and collapsibility index (CI) with right atrial blood pressure [3–5]. Assuming that the aortic (AO) diameter does not change significantly with the amount of circulating fluid, the IVC-to-AO ratio (IVC/AO) has been used as a further indicator of volume status also in pediatric ages [6–12]. The utility of this parameter in pediatric age is not yet defined and one of the greatest limitations is the lack of reference normal values by body

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https://doi.org/10.1016/j.jjcc.2019.02.021
0914-5087/

surface area (BSA). Moreover, in the acute setting the pre-illness weight is often not known; therefore the availability of normal values by age could be useful [10–15].

Once the Z-score of the IVC and AO and IVC/AO according to BSA and age will be defined, future studies will be able to evaluate the utility of these parameters in the assessment of intravascular volume.

The aim of the present cross-sectional study is to provide reference ranges for the sonographic measurement of IVC, AO, and IVC/AO in healthy Italian children.

Materials and methods

Subject enrollment

The study population consisted of 516 healthy young subjects aged between 1 month and 16 years prospectively enrolled between January and December 2016 in the Pediatric Echocardiography and Radiology Laboratory at the Foundation IRCCS Policlinico S. Matteo, University of Pavia. There were 254 males and 262 females.

Children included in the study had no clinical or objective signs of congenital or acquired disease or genetic syndromes. Most subjects were evaluated for the presence of cardiac murmur, chest or abdominal pain, cervical adenopathies, or for screening of genitourinary malformations. Exclusion criteria included the presence of a clinical history or objective finding of hypovolemia or any conditions thought to influence volume status (e.g. renal insufficiency, diabetes, etc.). Vascular course anomalies (e.g. chest or thoracic spine deformities) were also excluded.

Age, weight, height, and BSA [16] (Haycock formula) at the time of evaluation were recorded.

A written consent to the study as indicated by the Ethics Committee of our Institution was obtained for all patients. The study was performed in accord with the Good Clinical Practice guidelines as indicated by the "Declaration of Helsinki".

Echocardiographic examination

The evaluations were performed by 5 operators (1 radiologist, 3 pediatric cardiologists, and 1 US-accredited pediatrician).

All research staff underwent a 10-h training course consisting both of theoretical knowledge and practical experience. Before the enrolment of the overall population a sample of 30 subjects was evaluated by raters in order to assess the intra and interoperator reliability; Lin's concordance coefficient resulted to be excellent, with values over 0.90 (data not shown). A supervisor rated image quality and poor quality images were omitted from our analysis.

The examinations were performed with the child in the supine position during quiet passive respiration which was obtained by adopting many environmental measures and the collaboration of parents (music, video, colors, etc.) according to age of children. Ultrasound measurements were obtained using an Aloka ProSound α 10 (Hitachi, Japan), a Toshiba Model SSH–880 CV (Toshiba Japan), an Aloka ProSound α 6 (Hitachi, Japan), and an ESAOTE MyLab Twice (Esaote Italy) with curved probes (convex or microconvex). With the transducer placed just below the level of xyphoid bone, IVC and AO image in B-mode were obtained in transverse plane. Maximum systolic diameter in M-mode of the aorta (AOs) from inner wall to inner wall was then recorded. Then, moving the transducer just to the right shoulder of the subject, a sub-costal long-axis view of the IVC will be obtained including the IVC-right atrial junction and confluence of the hepatic veins. The minimum inspiratory and maximum expiratory diameter in M-Mode of IVC (IVC min, IVC max) were then digitally recorded with care to align perpendicular to anterior and posterior walls of the IVC. To get a standardized landmark for the overall age the measure was obtained near the transverse view of the left portal vein (Fig. 1). CI, defined as 100 $\times$ (IVC max $-$ IVC min)/IVC max was then obtained.

IVC/AO ratio was calculated for the AOs (IVC max/AOs).

Statistical analysis

Power considerations: a sample size of 500 subjects was needed in order to determine reference interval limits with a precision of 1–2% and with a 90% confidence interval. This way the lower limit (of the 5% of the reference interval) could vary between 3–4% and 6–7%, while the upper limit (of the 95% of the reference interval) could vary between 93–94% and 96–97%. Sample size was estimated using the method reported by Jennen-Steinmetz and Wellek [17].

Quantitative variables were described as mean and standard deviation (SD) as they were normally distributed (Shapiro test); qualitative ones as counts and percentages. Differences between two groups were analyzed by t-test for independent data, while one-way ANOVA, with Bonferroni correction for multiple testing, was used to explore differences among more than two groups.

Before calculating the reference values we performed a correlation analysis between the anthropometric parameters (age, BSA) and all the echocardiographic measurements (IVC max, IVC min, AOs, CI, IVC max/AOs). Correlation between quantitative variables was defined with Pearson r correlation coefficient.

In order to determine reference values for children aged $\leq$1 year the robust method described by the CLSI guidelines (2008) [18] was used. Considering the small 90% confidence intervals for upper and lower limits were calculated using the bootstrap – percentile interval method with a fixed number of interactions, as reported by Efron and Tibshirani [19].

In order to obtain a sufficient number of subjects to calculate a reliable reference range, we categorized children >1 year into 3-year classes ($1 < \text{age} \leq 4$, $4 < \text{age} \leq 7$, $7 < \text{age} \leq 10$, $10 < \text{age} \leq 13$, $13 < \text{age} \leq 16$).

For children aged over 1 year reference ranges were determined through the age-related approach reported by Altman [20], by Altman and Chitty [21], and by Wright and Royston [22]. Reference ranges for all the echocardiographic measurements were calculated using a parametric method.

In detail, the method included the following steps:

1. If the distribution of the measurements (the variable for which to establish a reference interval) showed skewness at different levels of age, the measurements are transformed logarithmically or using a Box-Cox power transformation.
2. The transformed measurements were modeled on age using weighted polynomial regression [21]. This regression model gave the mean of the (transformed) measurements as a function of age: mean (age).
3. The residuals of this regression model were calculated.
4. The absolute residuals, multiplied by $\sqrt{\pi/2}$ were modeled on age using weighted polynomial regression [20]. This second regression model gave the standard deviation of the (transformed) measurements as a function of age: SD (age).
5. For every age in the observed range, the reference interval was calculated by taking mean (age) $\pm z \times$ SD (age). For a 95% reference interval $z = 1.96$. If the data were initially transformed in step 1, the resulting values were back transformed to their original scale.
6. The model was evaluated by analyzing and plotting Z-scores for all observations. The Z-score for an observed value y is calculated by

$$z = \frac{y - \text{mean(age)}}{\text{SD(age)}}$$

The *Z*-scores should be normally distributed. Normal distribution was evaluated with Shapiro–Wilk test [23].

Reference values were then calculated for age and BSA. Linear regression models with interaction between age and gender were used to compare echocardiographic measurements between males and females.

For each echocardiographic measurement for children aged over 1 year the following centiles were provided: 1st, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, and 99th with the respective diagram, for overall sample. For synthetic reasons values were reported in tabular form for 3 year-classes.

The significance level was set at $\alpha = 0.05$ and all tests were two-sided.

Data analysis was performed with the STATA statistical package (release 14.0, 2015, Stata Corporation, College Station, TX, USA) and with MedCalc version 16.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

Results

Demographic and echocardiographic data

Demographic characteristics of the population are listed in Table 1 separately for children aged ≤1 year and in 3 year-classes for children aged >1 year: namely $1 < \text{age} \leq 4$, $4 < \text{age} \leq 7$, $7 < \text{age} \leq 10$, $10 < \text{age} \leq 13$, $13 < \text{age} \leq 16$.

Table 2 reports descriptive statistics with mean and SD for all the echocardiographic measurements separately for the same age classes.

Correlation between anthropometric parameters and echocardiographic measurements

Pearson *r* coefficients for the correlation between anthropometric parameters and echocardiographic measurements are reported in Table 3. IVC and AO diameters showed high positive correlation with all the parameters except body mass index (BMI). Lower correlation was found between age, height, weight, and BSA and the IVC/AO ratios, while CI had nearly no correlation with all the anthropometric parameters considered.

Reference ranges

Reference ranges were determined separately for children aged ≤1 year and for children aged over 1 year.

For children aged ≤1 year results are reported in Table 4, where for each measurement upper and lower limits with their 90% confidence intervals are reported.

For all the echocardiographic measurements for children aged >1 year, ranges are presented graphically in Supplemental Material – Fig. 1a–h where the main percentiles are plotted versus age.

Reference values are reported in tabular form too in Supplemental Material (Table 1).

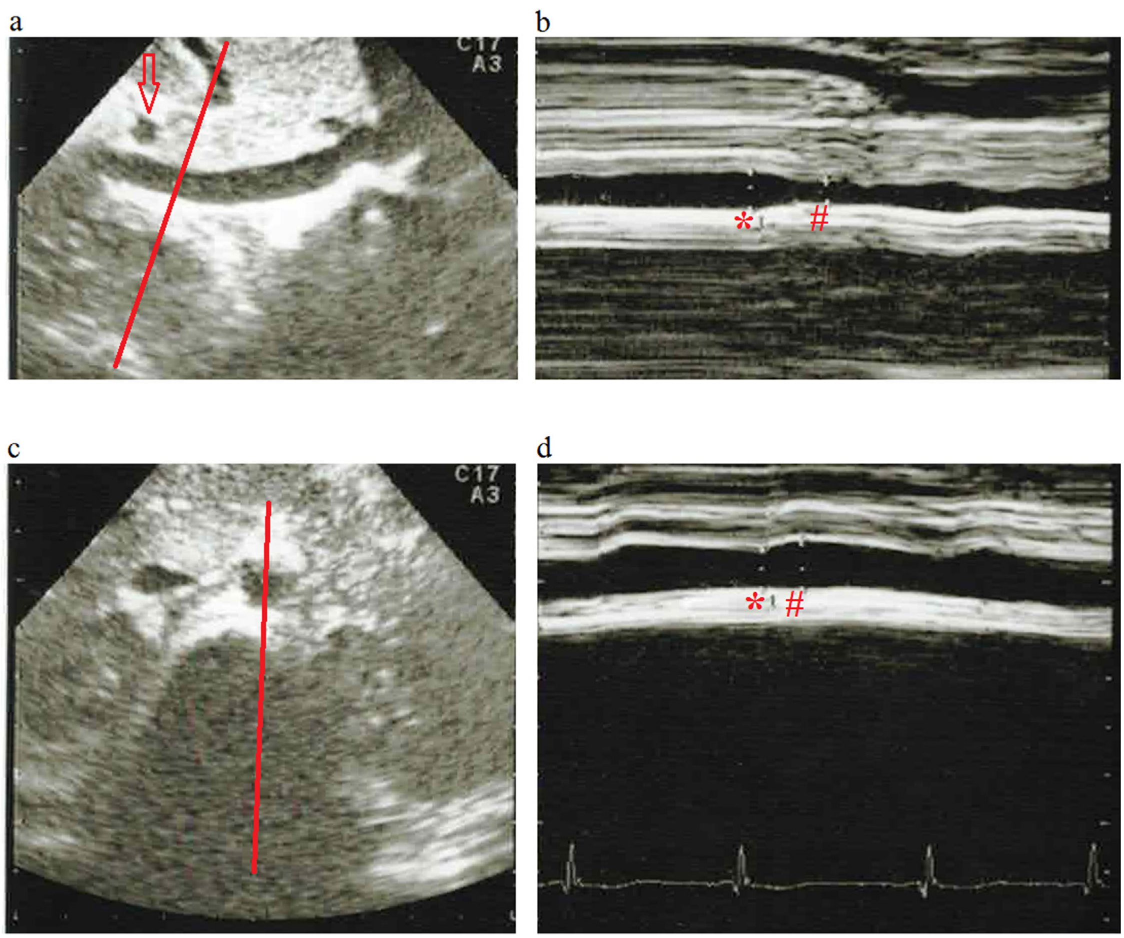

Fig. 1. IVC and AO image. (a) IVC image in B-mode: solid line indicates where the diameter is measured while the arrow indicate the transverse section of the left portal vein; (b) IVC image in M-mode: IVC max (*) and IVC min (#); (c) AO image in B-mode solid line indicates where the diameter is measured; (d) AO image in M-mode diastolic (*) and systolic AO (#).
IVC max, inferior vena cava maximum expiratory diameter in M-mode; IVC min, inferior vena cava minimum inspiratory diameter in M-mode; AO, aorta.

Table 1
Anthropometric parameters separately for age.

Age (years)	Weight (kg)	Height (cm)	BMI	BSA (m^2)	F/M
Age ≤ 1	6.45 (1.94)	63.09 (7.7)	15.93 (3.01)	0.32 (0.07)	29/25
1 < age ≤ 4	13.85 (5.58)	92 (13.78)	16 (2.37)	0.58 (0.16)	48/27
4 < age ≤ 7	19.55 (4.39)	111.46 (8.48)	15.67 (2.56)	0.77 (0.1)	46/71
7 < age ≤ 10	30.18 (7.86)	131.6 (8.82)	17.26 (3.27)	1.05 (0.15)	45/50
10 < age ≤ 13	39.68 (10.15)	146.95 (11.65)	18.15 (3.46)	1.27 (0.2)	49/50
13 < age ≤ 16	52.59 (9.03)	163.16 (8.24)	19.76 (3.06)	1.55 (0.15)	45/31

Data are reported as mean and SD.
All comparisons between boys and girls were statistically not significant.
BMI, body mass index.
BSA, body surface area.

Table 2
Echocardiographic measurements for the overall sample and for all the age classes.

	Overall (n = 516)	Age ≤ 1 (n = 54)	1 < age ≤ 4 (n = 75)	4 < age ≤ 7 (n = 117)	7 < age ≤ 10 (n = 95)	10 < age ≤ 13 (n = 99)	13 < age ≤ 16 (n = 76)
IVC max (mm)	11.6 (4.9)	5.0 (1.2)	8.1 (2.7)	9.7 (2.4)	12.5 (3.4)	14.5 (3.5)	17.9 (4.0)
IVC min (mm)	8.2 (4.4)	3.2 (1.1)	5.3 (2.7)	6.7 (2.6)	8.85(3.3)	10.4 (4)	13.5 (4.2)
AOs (mm)	11.1 (3.4)	6.3 (1.3)	8.7 (1.6)	9.8 (1.7)	11.9 (2.2)	13.5 (2.8)	15.0 (2.9)
CI (%)	31 (17)	36 (16)	36 (18)	31 (17)	30 (17)	30 (16)	25 (13)
IVC max/AOs	1.03 (0.28)	0.83 (0.20)	0.92 (0.19)	0.99 (0.22)	1.07 (0.30)	1.10 (0.27)	1.22 (0.31)

Data are reported as mean and SD.
IVC max, inferior vena cava maximum expiratory diameter in M-mode; IVC min, inferior vena cava minimum inspiratory diameter in M-mode; AOs, aorta systolic diameter in M-mode; CI, collapsability index.

Table 3
Correlation coefficients between anthropometric parameters and echocardiographic measurements.

Echocardiographic measurement	Age	BSA
IVC max	0.79	0.82
IVC min	0.71	0.72
AOs	0.79	0.83
CI	−0.21	−0.20
IVC max/AOs	0.41	0.40

Pearson r coefficients and p-values (if not $p < 0.001$) are reported.
All correlation coefficients were statically significant ($p < 0.001$) unless otherwise specified.
BSA, body surface area; IVC max, inferior vena cava maximum expiratory diameter in M-mode; IVC min, inferior vena cava minimum inspiratory diameter in M-mode; AOs, aorta systolic diameter in M-mode; CI, collapsibility index.

Table 4
Reference intervals of all echocardiographic measurements for children aged ≤1 year; upper and lower limits with a 90% confidence interval (90% CI) are reported.

Echocardiographic measurement	LL	90% CI	UL	90% CI
IVC max (mm)	3.0	2.5–3.4	7.0	6.5–7.4
IVC min (mm)	1.3	1.0–1.7	5.1	4.6–5.5
AOs (mm)	4.3	3.8–4.8	9.0	8.0–10.1
IVC max/AOs	0.47	0.38–0.54	1.14	1.05–1.22

IVC max, inferior vena cava maximum expiratory diameter in M-mode; IVC min, inferior vena cava minimum inspiratory diameter in M-mode; AOs, aorta systolic diameter in M-mode; LL, lower limit; UL, upper limit.

For children aged >1 year regression equations for mean and SD by age (years) are reported in Table 5, while regression equations by BSA (m^2) are reported in Table 6. All the Z-scores were normally distributed and the r^2 of the equation are all above 0.7 (data not shown).

Discussion

The assessment of intravascular volume status and right heart function in critically ill patients is challenging. Bedside ultrasound could be a useful additional non-invasive tool to estimate intravascular status and right atrial pressure (RAP) by measuring IVC diameter and CI in adults [3–5,24–26].

Moreover, the correlation between the IVC to AO diameter has received much interest in pediatrics [8,9]. One of the major limits of these studies is the lack of reference normal values in pediatric subjects.

Haines et al. described a sample of 25 patients ranging from 13 months to 20 years (mean 102 months). Kathuria et al. enrolled 63 patients ranging from 2 to 22 years grouped into three age classes. Munk et al. defined infrarenal aorta diameter in 176 healthy children from 1 to 16 years of age [27–29].

We present a cross-sectional study of the sonographic measurements of the IVC and AO diameters in a wider sample of 516 healthy normovolemic children.

In agreement with data reported in literature [27,28], our study confirms the high positive correlation between all the diameters and age. This relationship is also confirmed for the other anthropometric parameters (height, weight, and BSA); only BMI showed a weaker correlation. Moreover, unlike what was reported by Munk et al. [29], we found no significant differences between males and females.

In the literature, predicted values of echocardiographic variables are expressed as Z-scores according to BSA [13,30], but, unfortunately, in emergency conditions weight is often not available. Our data showed a high concordance between Z-scores calculated according to BSA and age, therefore we think age could be used as an independent variable.

In previous studies IVC and AO diameters were measured both in B-mode [8,29] and in M-mode [27]. We suggest the use of M-mode because it can better differentiate the two phases of the aortic cycle and the respiratory excursion of the IVC, especially in the youngest age group with small vessels. Physiologically, the vessels' diameter is the result of the interaction between intravascular fluid volume and the compliance of the wall. The IVC is a highly compliant vessel and many factors can influence its diameter [31]. Several studies based on IVC are commonly used in clinical practice and in experimental studies for RAP estimation in adults. A positive correlation of the mean IVC diameter with the

Table 5
Regression equations to obtain, from age (years), mean and SD for the echocardiographic measurements, for patients aged over 1 year.

	Equation for mean	Equation for SD
IVC max (mm)	$5.5715 + 0.8748\ Age - 0.01730\ Age^2 + 0.0009866\ Age^3$	$1.4578 + 0.1629\ Age + 0.001255\ Age^2$
IVC min (mm)	$2.8958 + 0.8955\ Age - 0.03867\ Age^2 + 0.001785\ Age^3$	$1.2923 + 0.2488\ Age - 0.001999\ Age^2$
AOs (mm)	$7.4852 + 0.3000\ Age + 0.03776\ Age^2 - 0.001541\ Age^3$	$1.0719 + 0.09379\ Age + 0.002646\ Age^2$
IVC max/AOs	$0.7579 + 0.07569\ Age - 0.006886\ Age^2 + 0.0002597\ Age^3$	$0.1601 + 0.009179\ Age + 0.0001512\ Age^2$

IVC max, inferior vena cava maximum expiratory diameter in M-mode; IVC min, inferior vena cava minimum inspiratory diameter in M-mode; AOs, aorta systolic diameter in M-mode.

Table 6
Regression equations to obtain, from BSA (m^2), mean and SD for the echocardiographic measurements, for patients aged over 1 year.

	Equation for mean	Equation for SD
IVC max (mm)	$1.6172 + 10.1956\ BSA + 0.9556\ BSA^2 - 0.5915\ BSA^3$	$-0.005186 + 3.3012\ BSA - 0.5107\ BSA^2$
IVC min (mm)	$1.8827 + 1.6773\ BSA + 8.1362\ BSA^2 - 2.9661\ BSA^3$	$-0.1707 + 3.9434\ BSA - 0.6478\ BSA^2$
AOs (mm)	$2.6323 + 11.9961\ BSA - 3.8559\ BSA^2 + 0.8650\ BSA^3$	$0.7079 + 0.6557\ BSA + 0.4178\ BSA^2$
IVC max/AOs	$0.7023 + 0.3882\ BSA + 0.009391\ BSA^2 - 0.03838\ BSA^3$	$0.1822 - 0.02477\ BSA + 0.08030\ BSA^2$

BSA, body surface area; IVC max, inferior vena cava maximum expiratory diameter in M-mode; IVC min, inferior vena cava minimum inspiratory diameter in M-mode; AOs, aorta systolic diameter in M-mode.

central venous pressure (CVP) has been demonstrated [3,5,24]. The increasing IVC mean diameter seems to predict a higher risk of heart failure while a contraction of intravascular volume is proved to result in measurable decreases in the diameter [31–35]. However, many hemodynamic and instrumental factors influence the IVC measure and in the literature there is much controversy about its use [36]. Recently, Patel et al. showed that not the diameter but IVC systolic flow velocity provided the best non-invasive estimate of normal RAP in infants and children [37], validation studies in children are currently limited but it was recently suggested that IVC parameters might be indexed to BSA to allow comparison within the pediatric population [14].

Our data showed a wide range of its diameter and it could be useful to know its upper and lower limit rather than the absolute value within each age class.

Moreover, although also CI resulted to have a high variability in overall sample and in each age class, we detected a weak correlation with age and with all the anthropometric parameters analyzed. The mean observed CI value in normovolemic children, breathing spontaneously was 30% (SD 17%) in children >1 year and 36% (SD 16%) in children <1 year.

Other studies based on CI indicate an inverse relationship between the CI to CVP: a CI >40% is considered an acceptable cut-off to predict fluid responsiveness in spontaneously ventilating adults patients while CI <15% seems to be predictive of fluid unresponsiveness [38]. However, there is no clear evidence that supports a linear relationship between CI and CVP, instead there is an inverse relationship when CI values are either very high or low [39]. There are few studies that analyzed the validity of CI as a predictor of fluid responsiveness or the dehydration condition in children. Long et al. found in the PREDICT study no significant correlation between CI and fluid responsiveness at 5 or 60 min in spontaneously ventilating children with sepsis [40]. The BUDDY study suggests that there is little utility to using the ultrasound-measured CI in the assessment of children with possible dehydration [11].

Weber et al. confirmed a low predictability of IVC diameter variation to determine fluid responsiveness during mechanical ventilation in the pediatric patient population [41].

Our results could help to verify the relationship between CI and CVP and to identify a cut-off value able to evaluate significant changes in intravascular volume or RAP but further studies in pediatric ages are needed.

Unlike the IVC, the aorta is a vessel with low compliance and therefore less affected by intravascular changes. Chen et al. [8] showed that systolic aortic diameter does not change before and after hydration and Yanagawa reported that mean aortic abdominal diameter remained constant despite large blood losses [42]. These data suggest the use of IVC/AO ratio, rather than the IVC diameter alone in some conditions. We found the IVC max/AOs mean value of 1.03 (SD 0.28). Similar data were reported by Kwon et al. with a median (IQR) value of 1.09 (0.86, 1.60) and by Durasjka et al. in adult subjects (mean 1.2, SD 0.17) [43,44]. However we have noticed age-dependent mean values from 0.83 (SD 0.20) age <1 year and 0.92 (SD 0.19) in younger subjects (1–3 years) to 1.22 (SD 0.31) in older subjects (13–16 years). Most of the previous studies presumed that IVC/AO ratio was independent of age or body size [27,28], but although IVC/AO ratio is a relative measurement our data showed some influence by anthropometric parameters. Actually, we found a greater age-dependent increase in IVC diameter compared to the AO that would explain the variations of this relationship over time. Future studies are needed to improve the diagnostic utility of IVC/AO ratio if the age-adjusted normal value of IVC/AO are adopted.

Study limitations

The principal limitation of the study is the use of a specific population (Italian, Caucasian) without different races and ethnicities. However, the use of a homogeneous cohort makes it possible to derive normal values for this specific population.

Data were collected on children assumed to be euvolemic based on their clinical history and vital signs: this process may have introduced a bias and several subjects may also have an individual variability in oral intake. Further studies are necessary to derive reference ranges for low volume status.

A wider sample of children ≤1 year would be useful to better and more deeply study reference ranges eventually discriminating by months. Anyway, no other reference values for this specific class of age are reported in the literature.

Conclusions

Our data show that both *Z*-scores (or percentiles) calculated according to BSA and age could be used as reference ranges in Caucasian Italian pediatric population; therefore, reliable reference ranges for IVC, AO, and IVC/AOs in healthy children were provided. IVC/AOs showed age-dependent values which must be considered while evaluating pediatric patients.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2019.02.021.

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