Clinical Nutrition 39 (2020) 1411–1417

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Reference values for the phase angle of the electrical bioimpedance: Systematic review and meta-analysis involving more than 250,000 subjects

Rita Mattiello [a, b, *], Mariana Azambuja Amaral [a, c], Eduardo Mundstock [a, d], Patrícia Klarmann Ziegelmann [b]

[a] Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Brazil
[b] Programa de Pós-Graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul (UFRGS), Brazil
[c] Centro Universitário Ritter dos Reis/UniRitter, Brazil
[d] Prefeitura de Canela, Brazil

A R T I C L E   I N F O

Article history:
Received 17 May 2019
Accepted 3 July 2019

Keywords:
Phase angle
Bioimpedance
Reference values

S U M M A R Y

Background & aims: The bioimpedence phase angle has been considered as a predictor for morbidity and mortality in different clinical situations, although reference values from a large healthy population are lacking. The aim of this meta-analysis is to estimate mean phase-angle values in healthy individuals.
Methods: This meta-analysis systematically searched MEDLINE, EMBASE, The Cochrane Controlled Trials Register, SCIELO, LILACS, CINAHL, Web of Science and gray literature for studies estimating mean phase angles. Quality of evidence was assessed for all studies and subgroup (males and females) meta-analysis stratified by age group according to literature (up to 2; 3–5; 6–12; 13–15; 16–18; 19–28; 29–38; 39–48; 49–58; 59–69; 70–80 and >80 years of age) were conducted using random-effects models.
Results: A total of 46 studies including 249,844 subjects were selected for the present analysis. Males show a pooled estimate of the mean phase angle of 3.6 (95% CI: 3.0–4.1) for infants (0–2 y), increasing progressively to 7.3 (95% CI: 7.0–7.5) at the teenage phase (16–18 y), stabilizing during adult ages (18–38) and decreasing progressively with ongoing years with an estimate of 5.3 (95% CI: 4.5–6.0) for elderly above 80 years old. Similarly, females start from 3.7 (95% CI: 3.2–4.3) for infants (0–2 y), increasing progressively to 6.4 (95% CI: 6.1–6.8) at the teenage phase (16–18 y), stabilizing during adult ages (18–48) and decreasing progressively with ongoing years with an estimate of 5.4 (95% CI: 5.3–5.6) for elderly above 80 years old. Also, males have higher estimates than females for all age groups except for infants (0–2) and subjects older than 80 years old. Heterogeneity was high for all age groups.
Conclusions: In both sexes, phase-angle values have a similar pattern that start from infants, increase progressively up to the teenage phase, stabilize during adult ages, and then decrease progressively in older subjects and the elderly.
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1. Introduction

The bioimpedance phase angle has been considered as an important predictor of health status in different clinical situations. It is obtained through the relationship between direct measures of resistance (R) and reactance (Xc) from bioelectrical impedance analysis. Low phase-angle values have been associated with cell death or with a change in selective permeability of the membranes, which in turn compromise their integrity. It is known that inflammation, disease, malnutrition, functional disabilities and healthy life stale can result in disturbed electric tissue properties, consequently affecting the phase angle [1–3].

Recently, evidences show that subjects with acute and chronic disease have lower phase-angle values than healthy individuals, which may predict worse health outcomes [4–6], including mortality [1,7]. Therefore, lower phase angle seems to be a prognostic factor predicting mortality in patients with liver cirrhosis [8], with

* Corresponding author. Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Avenida Ipiranga 6690, 2nd Floor, Porto Alegre 90610-000, RS, Brazil. Fax: +55 51 3320 3312.
E-mail address: rita.mattiello@pucrs.br (R. Mattiello).

https://doi.org/10.1016/j.clnu.2019.07.004
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chronic obstructive pulmonary disease [9], undergoing hemodialysis [10] and with cancer [7].

The phase angle is dependent on the capacitive behavior of tissues associated with cellularity, cell size and integrity of the cell membrane. Therefore, phase-angle reference values are mandatory for the assessment of individual deviations from the population average [11–13]. However, reference values from a large healthy population, with data from the first years of life to the most advanced ages, are lacking. Hence, the aim of this meta-analysis is to estimate phase-angle values for healthy individuals from both sexes and for different ages.

2. Subjects and methods

This systematic review and meta-analysis were performed following the PRISMA guidelines [14], and its protocol was registered in the PROSPERO database as CRD42018063875.

2.1. Eligibility criteria

The inclusion criteria for studies included the following: (i) healthy individuals of any age and sex; (ii) all types of study designs; (iii) any language; and (iv) the study reported mean bioimpedance phase angle separated by sex and age. Case and review studies, case series, experimental models, responses letters, editorials and duplicated publications were excluded. A study was considered as duplicate if it was from the same study group with the same inclusion date and individual characteristics. In case of duplicated studies, the study with the larger sample size was considered.

2.2. Information sources

The following databases, from inception to October 2018, were used to search the literature: MEDLINE (via PUBMED), EMBASE, Cochrane The Cochrane Controlled Trials Register (CCTR) Scientific Electronic Library Online SCIELO, Latin American Caribbean Health Sciences Literature (LILACS via BIREME), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Web of Science (Thomson Reuters). The MEDLINE search strategy was created and adapted for the other databases. Additional references were searched by crosschecking bibliographies of retrieved full-text papers. Gray literature was also searched by writing to leading experts in the field and checking reference lists of other systematic reviews. Studies published in any language were included. Detailed information on the search strategy is reported in supplementary material (Table S1).

2.3. Study selection

Two review authors (RM and EM) independently scanned the abstract and title of each study from the search results. All potentially relevant articles were investigated as full texts. In both phases, wherever differences in opinion existed, a third author (MA), who initially did not evaluate the articles, reviewed it to reach a final decision between the three authors. For studies that fulfilled the inclusion criteria, three authors worked on extracting the data. RM did the extraction of all articles and, independently, MA and EM split the whole as a second extractor.

2.4. Data extraction and quality appraisal

The following information for each study was collected: author, year of publication, country and language. The following information from the study population was obtained: age, sex, ethnicity and BMI. Study methods and characteristics included the study design, bioelectrical impedance equipment characteristics, sample inclusion and exclusion criteria. Primary data were the phase angle and factors that were used to adjust the analyses. Authors were contacted to obtain missing data regarding phase-angle means, standard deviation (or error) and sample size by sex, when necessary. Quality of individual studies was assessed independently by two review authors (RM and EM) according to the National Institute of Health for observational cohort and cross-sectional studies [15]. Publication bias was assessed graphically (Figure S1).

2.5. Statistical analysis

Phase-angle means were pooled using meta-analysis for single-arm studies with random-effects models. Metanalyses were fitted separately for males and females and for each age group (up to 2; 3–5; 6–12; 13–15; 16–18; 19–28; 29–38; 39–48; 49–58; 59–69; 70–80, and >80 years of age). Age groups were defined according to previously described literature [16–18]. The results were presented as pooled means with a 95% confidence interval (CI). The heterogeneity among studies was assessed using the Q-Cochran test and I^2 statistics. We planned to explore heterogeneity using race as a factor, but this was not performed since the studies did not provide sufficient data. For longitudinal and clinical trials studies that assessed phase angle in more than one moment, the values from the baseline evaluation were the ones considered. The review authors were aware that some issues suitable for sensitivity analysis were only identified during the review process when the individual peculiarities of the studies under investigation were identified. At this phase of our review, we performed a sensitivity analysis to assess the robustness of our analyses by including only the studies with good quality. The meta-analysis was performed using the Meta R package (https://CRAN.R-project.org/package=meta).

3. Results

The search strategy identified 549 articles. From this total, the 122 duplicates and 254 that did not address the research topic were excluded, leaving 427 for assessment of titles and abstracts. At this phase, 254 articles that did not address our research question, 4 that were duplicates and 36 other studies were excluded leaving 133 for full-text reading. Fifty studies were eventually included in this review since 84 studies were excluded because they did not describe essential information (e.g., absolute values for phase angle by sex) (Fig. 1). The percentage of disagreement between the evaluators during the full-text phase was 24%.

3.1. Characteristics of included studies

Twenty studies were conducted in European countries [10,11,18–35]. Participants' ages ranged from 13 days [36] to >80 years [21], and 17 studies included only one sex: females [20,22,26,37–42] or males [23,28,32,33,43–45]. Ethnicity was not described in most of studies; of the 6 studies that described it, White/Caucasian participants were more frequently mentioned [11,18,34,46–48]. The mean BMI ranged from 13.8 [36] in young children to 49.1 in adult subjects [38]. (Tables 1 and S2).

The participants' inclusion criteria vary according to the target population addressed by the studies. Most participants were recruited for convenience in communities, schools, universities, sports centers, hospitals, outpatient clinics and clubs. Exclusion criteria were essentially the ones that contraindicated the bioimpedance (Table 1 and S2).

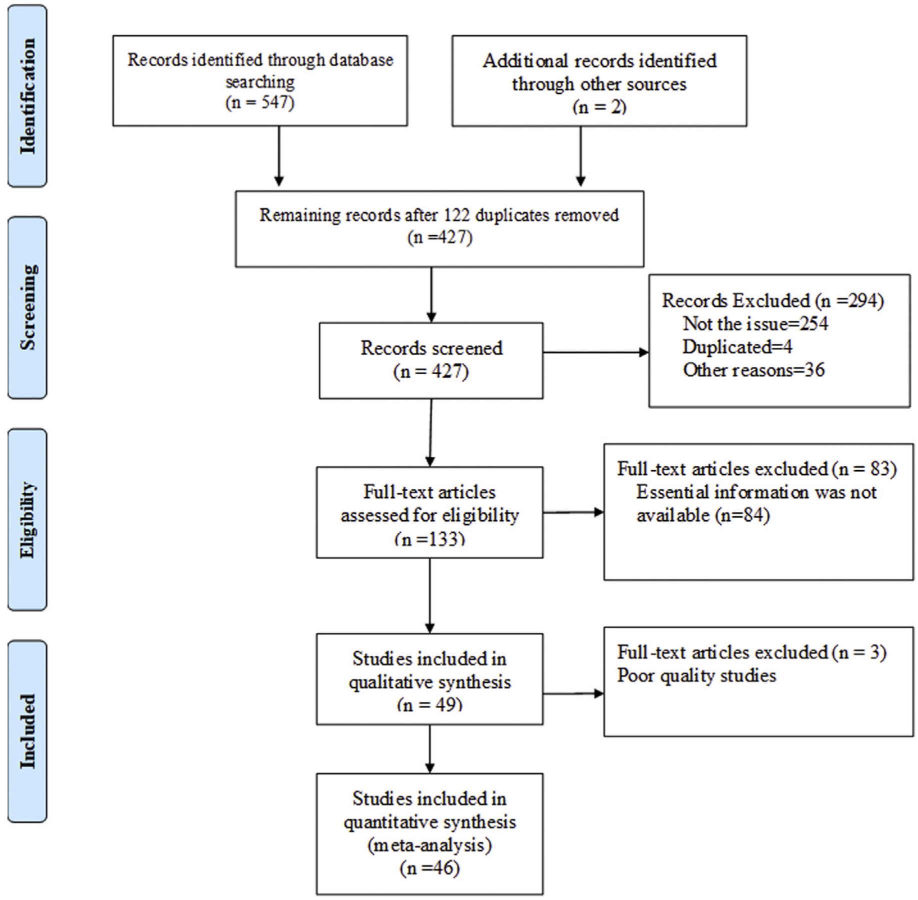

Fig. 1. Study flow diagram.

Five studies were clinical trials [22,26,37,41,49], and the remaining were observational, 3 of which had a follow-up [31,33,38]. The mean phase angle was described, adjusted by or associated with sex in a majority of studies (64%) [6,10–12,17–19,21,24,25,27,29,30,34–36,46–60]. However, less than half of the studies considered participant age [9,11,12,17,18,20,24,25,27,29,34,35,44,46–48,50,53,54,56,57,60].

In general, the included studies considered different variables for adjustments or associations with phase angle according to the objective of the study.

The description of the equipment (e.g., electrode characteristics), frequencies and currents varied between studies, and this information was not done in a standardized way (Table S4). The equipment from RJL Systems and/or ARKEN companies were the most frequently used [6,11,17–19,21–24,27–29,31,35,36,43,46,47,50,54,56,58]. Equipment frequency and current used were not stated in the majority of studies [40,41,46,49,50]. However, after consulting the device manuals and models described in the articles, as well the authors, we identified that all used a frequency of 50 kHz for phase angle measurement. The studies did not report the type of electrodes used and/or their placement [6,17,22,23,29,31,37,47,48,50,61].

3.2. Meta-analysis

Only 3 studies were rated as poor quality [31,39,52], and we did not include than in the meta-analysis (Table S4).

The pooled estimate means for phase angle was calculated using data retrieved from 46 studies including 249,844 subjects. Of this total, 200,536 (81%) were female, and the number of participants per age group was 0–2: 688 (0.3%); 3–5:1381 (0.5%); 6–12: 3218 (1.3%); 13–15:1354 (0.5%); 16–18: 4828 (1.9%); 19–28: 43,479 (17.4%), 29–38: 61,333 (24.5%); 39–48: 55,344 (22.1%); 49–58: 44,239 (17.7%), 59–69: 23,520 (9.6%); 70–80: 10,242 (4.0%) and >80: 218 (0.08%). There was no evidence of funnel plot asymmetry (Figure S1).

Males show a pooled estimate mean phase angle of 3.6 (95% CI: 3.0–4.1) for infants (0–2y), increasing progressively to 5.6 (95% CI: 5.5–5.6) for 3–5y, to 6.0 (95% CI: 5.7–6.3) for 6–12y, to 6.4 (95% CI: 6.1–6.6) for 13–15y and to 7.3 (95% CI: 7.0–7.5) at the teenage phase (16–18y). Then, stabilizing during adult ages: 6.9 (95% CI: 6.6–7.2) for 19–28y, 7.2 (95% CI: 6.9–7.4) for 29–38y, and 7.0 (95% CI: 6.7–7.4) for 39–48. At this age the values start to decrease progressively with ongoing years: 6.5 (95% CI: 6.0–6.9) for 49–58y, 6.5 (95% CI: 6.2–6.8) for 59–69y, 5.6 (95% CI: 4.8–6.4) for 70–80y and 5.3 (95% CI: 4.5–6.0) for elderly above 80 years old. Similarly, females start from 3.1 (95% CI: 3.2–4.3) for infants (0–2y), increasing progressively to 5.4 (95% CI: 5.3–5.4) for 3–5y, to 5.9 (95% CI: 5.7–6.13) for 6–12y, to 6.3 (95% CI: 6.0–6.6) for 13–15y and to 6.4 (95% CI: 6.1–6.8) at the teenage phase (16–18y). Then, stabilizing during adult ages: 6.1 (95% CI: 5.9–6.3) for 19–28y, 6.2 (95% CI: 6.0–6.4) for 29–38y, and 6.3 (95% CI: 6.0–6.6) for 39–48. At this age the values start to decrease progressively with ongoing years: 5.9 (95% CI: 5.4–6.3) for 49–58y, 5.6 (95% CI: 5.4–5.8) for 59–69y, 5.1 (95% CI: 4.7–5.5) for 70–80y and 5.4 (95% CI: 5.3–5.6) for elderly above 80 years old (Fig. 2 and Figures S2-S9 and Table S5).

For both sexes, statistical heterogeneity was high for most of the age groups. I^2 statistics varied from 97% to 100% for males and from 97% to 100% for females. The only group that had low ($I^2 = 0\%$)

Table 1
Characteristics of included studies.

First author	Country	Sex	n Male	n Female	Age Male	Age Female	BMI Male	BMI Female	Study design
Saad MAN, 2018 [6]	Brazil	Male, female	103	299	69.7 ± 6.8	70.7 ± 6.9	28.2 ± 4.4	28.8 ± 5.6	Cross-sectional
Genton L, 2017 [10]	Switzerland	Male, female	816	491	72.0 ± 9.2	72.8 ± 10.0	23.7 ± 5.9	22.2 ± 7.0	Retrospective
Bosy-Westphal A, 2006 [11]	Germany	Male, female	30,750	183,982	44.6 ± 13.5	42.5 ± 13.2	31.5 ± 5.0	30.2 ± 5.5	Cross-sectional
Espinosa-Cuevas ML, 2007 [12]	Mexico	Male, female	204	235	47.1 ± 16	42.4 ± 13	25.6 ± 2.7	24.8 ± 2.8	Cross-sectional
Barufaldi LA, 2011 [17]	Brazil	Male, female	1621	1583	10.8 ± 2.9	10.8 ± 2.9			Cross-sectional
Kyle UG, 2001 [18]	Switzerland	Male, female	2735	2490	51.1 ± 5.1	51.1 ± 5.1	23.9 ± 2.8	22.5 ± 3.4	Cross-sectional
Bonaccorsi G, 2009 [19]	Italy	Male, female	239	210	8	8	17.6 ± 3.0	17.9 ± 3.2	Cross-sectional
Buffa R, 2002 [20]	Italy	Female		143		11.9 ± 1.17		18.7 ± 2.4	Cross-sectional
Buffa R, 2003 [21]	Italy	Male, female	97	104	72.7 ± 7.1	73.4 ± 7.6	28.2 ± 3.7	29.5 ± 5.0	Cross-sectional
Campa F, 2018 [22]	Italy	Female	30			66.1 ± 4.7		30.6 ± 5.3	Randomized Clinical Trial
Campa F, 2018 [23]	Italy	Male	201		26.1 ± 5.4		23.7 ± 2.0		Cross-sectional
De Palo T, 2000 [24]	Italy	Male, female	97	120	14.5 ± 1.5	14.5 ± 1.5	20.0 ± 2.0	20.9 ± 2.2	Cross-sectional
Dittmar M, 2003 [25]	Germany	Male, female	244	409	61.0 ± 0.6	61.4 ± 0.5	25.9 ± 0.3	26.1 ± 0.3	Cross-sectional
Dos Santos L, 2016 [26]	Portugal	Female	33			68.7 ± 5.7		27.6 ± 4.8	Clinical trial
Genton L, 2018 [27]	Switzerland	Male, female	808	875	74.5 ± 7.7	77.4 ± 8.2	24.7 ± 3.7	24.5 ± 4.8	Retrospective
Giorgi A, 2018 [28]	Italy	Male	525		30.1 ± 11.3		22.2 ± 2.3		Cross-sectional
Ibanez ME, 2015 [29]	Italy and Spain	Male, female	227	213	40.9 ± 7.3	42.5 ± 7.1	26.4 ± 4.1	26.8 ± 5.6	Cross-sectional
Malecka-Massalska T, 2012 [30]	Poland, Taiwan	Male, female	32	32	23.4 ± 3.5	23.4 ± 3.5	23.0 ± 2.6	23.0 ± 2.5	Observational
Mascherini G, 2015 [31]	Italy	Male			21.8 ± 3.0				Prospective
Micheli ML, 2014 [32]	Italy	Male	893		24.1 ± 5.1		23.3 ± 1.6		Cross-sectional
Piglowska M, 2016 [33]	Poland	Male	55		60.3 ± 9.9		26.1 ± 3.2		Cohort
Tanabe RF, 2012 [34]	Italy	Male, female	129	126	0.87 ± 0.72	0.99 ± 0.79	17.0 ± 1.4	16.7 ± 1.4	Cross-sectional
Savino F, 2004 [35]	Italy	Male, female	90	63	13.4 ± 8.8	15.1 ± 8.0	15.6 ± 1.7	15.4 ± 1.7	Cross-sectional
Margutti AVB, 2010 [36]	Brazil	Male, female	52	57	0.03 ± 0.01	0.03 ± 0.01	13.8 ± 1.2	14.0 ± 1.0	Cross-sectional
Barbosa CD, 2018 [37]	Brazil	Female		30		54.5 ± 4.9		26.2 ± 2.8	Randomized Clinical Trial
Carrasco-Marginet M, 2017 [38]	Spain	Female		49		14.6 ± 1.4		49.1 ± 7.0	Pre-post quasi-experimental
Kim C–H, 2010 [39]	Korea	Female	22			20.9 ± 1.4		19.3 ± 0.7	Cross-sectional
Ribeiro AS, 2017 [40]	Brazil	Male, female	28	31	22.2 ± 4.3	23.2 ± 4.1	22.4 ± 2.4	22.0 ± 3.5	Prospective
Souza MF, 2017 [41]	Brazil	Female		41		67.2 ± 4.5		26.6 ± 4.8	Randomized Clinical Trial
Tomereli CM, 2018 [42]	Brazil	Female		155		67.7 ± 5.7		27.0 ± 4.4	Cross-sectional
Koury JC, 2018 [43]	Brazil	Male		40	13.4 ± 0.6		18.6 ± 1.5		Cross-sectional
Koury JC, 2014 [44]	Brazil	Male		195	23.3 ± 1.4		20.9 ± 2.9		Cross-sectional
Rodriguez–Rodriguez F, 2016 [45]	Colombia	Male	223		27.0 ± 10		22.8 ± 2.9		Cross-sectional
Barbosa-Silva MCG, 2005 [46]	United States	Male, female	832	1135	46.3 ± 18.3	48.1 ± 17.7	25.6 ± 4.2	26.0 ± 6.4	Cross-sectional
Gonzalez MC, 2016 [47]	United States	Male, female	599	843	43 ± 22.2	43 ± 22.2	25.3 ± 5.4	25.6 ± 5.4	Cross-sectional
Kuchnia AJ, 2017 [48]	United States	Male, female	3235	3002	31.4 ± 10.0		27.3 ± 5.7		Cross-sectional
Ribeiro AS. 2017 [49]	Brazil	Female		76		68.4 ± 5.5		27.2 ± 4.7	Clinical trial
Glew RH, 2003 [50]	Nigeria	Male, female	164	176	7.4 ± 3.4	8.6 ± 3.2	15.0 ± 2.9	14.9 ± 1.4	Cross-sectional
Ibrahim F, 2004 [51]	Malaysia	Male, female	51	91	29.4 ± 10.8	27.2 ± 9.1			Cross-sectional
Kumar S, 2012 [52]	India	Male, female	32	10	32.6 ± 12.2	32.6 ± 12.2	22.3 ± 3.42	22.3 ± 3.42	Cross-sectional
Martirosov EG, 2007 [53]	Moscow	Male, female	500	446	13.1 ± 1.9	13.1 ± 1.8			Cross-sectional
Mathias-Genovez MG, 2016 [54]	Brazil	Male, female	255	312	13.5 ± 2.1	13.4 ± 2.1	18.6 ± 1.5	18.9 ± 1.6	Cross-sectional
Nescolarde L, 2013 [55]	Cuba	Male, female	1538	1688	13–80	13–80	23.1 ± 2.1	22.6 ± 2.1	Cross-sectional
Saragat B, 2014 [56]	Italy	Male, female	265	295	77.0 ± 7.2	76.0 ± 7.1	26.4 ± 3.3	26.6 ± 4.1	Cross-sectional
Siddqui NI, 2016 [57]	India	Male, female	32	53	17–24	17–24	22.8 ± 3.8	22.3 ± 5.0	Cross-sectional
Toffano RBD, 2017 [58]	Brazil	Male, female	73	77	1.5 ± 0.6	1.5 ± 0.6	16.1 ± 1.4	15.3 ± 1.5	Cross-sectional
Veitia WC, 2017 [59]	Cuba	Male, female	620	323	22.7 ± 4.1	22.3 ± 3.5	24.0 ± 3.0	23.0 ± 2.0	Cross-sectional
Yamada Y, 2017 [60]	United States	Male, female	13	44	48.8 ± 12.4	52.0 ± 14.8	30.6 ± 8.4	32.6 ± 11.1	Cross-sectional
De França NAG, 2016 [61]	Brazil	Male, female	97	396	53.6 ± 10.7	53.6 ± 10.7	30.0 ± 5.8	30.0 ± 5.8	Cross-sectional

heterogeneity in both sexes was the group aged 80 years and above. By including only studies with good quality, the sensitivity analysis did not change the heterogeneity results. The lowest I^2 value identified by the sensitivity analysis was $I^2 = 99\%$.

There no evidence of publication bias (Figure S1).

4. Discussion

In our systematic review and meta-analysis, mean phase angles were estimated for healthy individuals of both sexes and with different ages. For the first time, it was demonstrated that, for both sexes, there is a progressive increase in the mean phase angle, starting at the first years of life until approximately the age of 18. It then stabilizes until adulthood at 7.3 for men and 6.4 for women. Finally, values progressively decrease after 48 years of age.

Different mechanisms are involved in the process that leads to higher phase-angle values, reflecting better integrity and functionality of the cell membrane, intracellular composition and enhanced tissue capacity. The process of growing up involves quantitative and qualitative bodily changes, which are reflected in phase-angle values [16,20]. Thus, when interpreting bioelectrical measures in children and adolescents, particularly during puberty, which is characterized by dramatic changes that occur at different times among individuals, we must acknowledge that observed values may be temporary [13,17]. The opposite takes place in the aging adult, where cellular integrity becomes progressively compromised and tissue mass is lost, leading to a decrease in phase angle with increasing age. This situation may suggest that the phase angle is also an indicator of cell function and health [16,21,25,46,62]. Males have higher mean phase angles compared

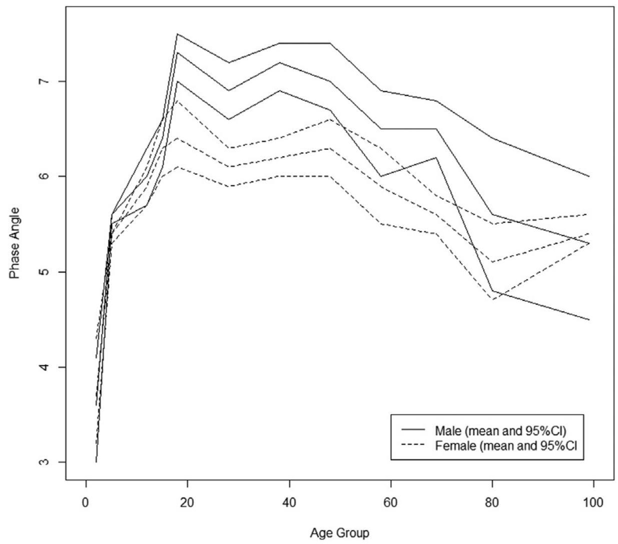

Fig. 2. Phase by sex and age.

to females. This can be explained due to the higher amount of body cell mass in males [11,25,63].

A low phase angle is an established parameter suggesting poor health prognosis [10,18,63]. The prognostic value may also differ between groups of patients with different clinical conditions since conditions such as infection, inflammation or disease-specific parameters may modify the phase angle [11,25,29,63]. A considerable number of studies have shown that the phase angle is a prognostic indicator for disease severity and mortality. However, the majority an important number of these studies did not consider the possible differences between sexes and age groups. Since phase-angle data is not usually available in a unique form, some authors use standardized phase-angle values (with cut-offs) derived from reference values from a specific population [16]. A major drawback of this method is that these cut-offs are not necessarily transferable to other populations and might not be applicable in the general clinical setting [16,63]. An alternative for the clinical interpretation of phase-angle results, particularly in the evaluation of interventions, could be the identification of the minimal important difference. Considering the mean difference between ages, health status, sex and age categories from the literature, we would suggest a clinically important phase-angle difference of 0.90° for females and 1.0° for males. Similar values have already been described in other studies with patients when comparing mean differences or suggested cut-offs between healthy and non-healthy groups [2,62].

There seems to be a difference in phase-angle values among different population characteristics, such as ethnic group, body mass and active vs. sedentary subjects [3,25,63]. We did not analyze those differences since very few of the included studies had all of this information, and factors considered in each study were different.

This study has some limitations. First, there exists population variability, since studies included different populations; however, this apparent limitation could be considered a strength due to the relevant sample size. The inclusion of participants with different characteristics improves the external validity of our study when using the data for the general population. The sensitivity analysis did not decrease the heterogeneity; nevertheless, the high statistical heterogeneity can be justified by the number of participants included in the studies. Most of the studies did not provide a bioimpedance analysis with sufficient detail or in a standardized manner, and this could have an impact on our results [27,62]. However, a large number of studies used the same apparatus. Future studies should include the technical specifications of the equipment used and describe the techniques used in a standardized manner to identify potential clinical differences in studies with representative population samples.

As shown in the analysis of the quality of studies was reasonable, but some items were poorly reported. A possible justification for this result is that some items from the quality scale used are more applicable to cohort studies than to cross-sectional studies, and most of the studies included in our analysis were cross-sectional. A major strength of our systematic review is the inclusion of all available studies by including gray literature in our search strategy as well as all major databases. We also did not limit the search by publication period or by language.

5. Conclusion

Our study found that, in both sexes, phase-angle values have a pattern where values increase progressively from the first years of life until 18 years of age, stabilize from 19 until 48 years and then progressively decrease thereafter. These estimates of mean phase-angle values in healthy individuals are important for clinical practice and research, whereas the use of bioimpedance phase angle can also contribute to the diagnosis and prognosis of health status as long as the different ages and sexes are considered in the interpretation of the results.

Funding

This study was financed in part by Fundação de Amparo à Pesquisa do Rio Grande do Sul (FAPERGS), the National Research Council of Brazil (CNPq) and, the Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior – Brasil (CAPES) – Finance Code 001.

Authors' contributions

Rita Mattiello: designed research, conducted research, provided essential reagents or provided essential materials, analyzed data or performed statistical analysis, wrote paper, and had primary responsibility for final content; Patrícia Klarmann Ziegelmann: designed research, conducted research, provided essential reagents or provided essential materials, analyzed data or performed statistical analysis, and wrote paper.

Mariana Azambuja Amaral: conducted research, provided essential reagents or provided essential materials, analyzed data or performed statistical analysis, and wrote paper.

Eduardo Mundstock: conducted research, provided essential reagents or provided essential materials, analyzed data or performed statistical analysis, and wrote paper.

Conflict of interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.07.004.

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