King's Research Portal

Document Version
Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Martin, L., Lagergren, J., Blomberg, J., A, J., Bosaeus, I., & Lagergren, P. (Accepted/In press). Phase angle as a prognostic marker after percutaneous endoscopic gastrostomy (PEG) in a prospective cohort study. *Scandinavian Journal of Gastroenterology*.

Citing this paper

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

General rights

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

Take down policy

If you believe that this document breaches copyright please contact librarypure@kcl.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

Phase angle as a prognostic marker after percutaneous endoscopic gastrostomy (PEG) in a prospective cohort study

Journal:	<i>Scandinavian Journal of Gastroenterology</i>
Manuscript ID	SGAS-2016-0168.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	07-Mar-2016
Complete List of Authors:	<p>Martin, Lena; Karolinska Institutet, Department of Molecular medicine and Surgery; Karolinska Institutet, Department of Biosciences and Nutrition; Karolinska Universitetssjukhuset, Department of Clinical Nutrition and Dietetics</p> <p>Lagergren, Jesper; Karolinska Institutet, Department of Molecular medicine and Surgery, ; King\'s College London Division of Cancer Studies</p> <p>Blomberg, John; Karolinska Institutet, Department of Clinical Science, Intervention and Technology (CLINTEC), ; Karolinska University Hospital, , Center for Digestive Diseases</p> <p>johar, asif; Karolinska Institutet, Department of Molecular medicine and Surgery,</p> <p>Bosaeus, Ingvar; Sahlgrenska University Hospital, Department Clinical Nutrition ; University of Gothenburg, Sahlgrenska Academy</p> <p>Lagergren, Pernilla; Karolinska Institutet, Department of Molecular medicine and Surgery; King\'s College London Division of Cancer Studies</p>
Keyword:	complications, early mortality, enteral nutrition, malnutrition

SCHOLARONE™
Manuscripts

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Phase angle as a prognostic marker after percutaneous endoscopic**
2
3 **gastrostomy (PEG) in a prospective cohort study**

4 **Short title: Phase Angle at time for PEG**

5
6 **Authors:** Lena Martin^{1,2,3}, RD, PhD., Jesper Lagergren^{4,5}, MD, PhD., John
7 Blomberg^{6,7}, MD, PhD., Asif Johar¹, Ingvar Bosaeus⁸, MD, PhD., Pernilla
8 Lagergren^{1,5}, RN, PhD.

- 9
10 1. Surgical Care Science, Department of Molecular medicine and Surgery, Karolinska
11 Institutet, Karolinska University Hospital, 17176 Stockholm, Sweden.
12 2. Department of Biosciences and Nutrition, Karolinska Institutet, Karolinska University
13 Hospital, 141 83 Huddinge, Sweden
14 3. Department of Clinical Nutrition and Dietetics, Karolinska University Hospital, 141 86
15 Stockholm, Sweden.
16 4. Upper Gastrointestinal Surgery, Department of Molecular medicine and Surgery,
17 Karolinska Institutet, SE-171 76 Stockholm, Sweden.
18 5. Division of Cancer Studies, King’s College London, London, United Kingdom.
19 6. Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinska
20 Institutet, Karolinska University Hospital, 141 83 Huddinge, Sweden
21 7. Center for Digestive Diseases, Karolinska University Hospital, SE-141 86 Stockholm,
22 Sweden.
23 8. Department Clinical Nutrition at Sahlgrenska University Hospital, Sahlgrenska Academy at
24 University of Gothenburg, Gothenburg, Sweden
25

Corresponding author:

Lena Martin, Registered dietician and PhD

Surgical Care Science, Department of Molecular medicine and Surgery,

Karolinska Institutet, Karolinska University Hospital, 17176 Stockholm, Sweden

e-mail address: lena.martin@ki.se

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

33 **Abstract**

34 **Objective:** The phase angle identifies changes in tissue’s electrical properties assessed by
35 bioelectrical impedance measurement and it can predict prognosis in some conditions.

36 Percutaneous endoscopic gastrostomy (PEG) is commonly used in patients with severe
37 nutritional problems, but there is a need to improve the clinical decision-making for using
38 PEG. We examined if a decreased phase angle predicts complications, short-term mortality
39 ([within 60 days of PEG insertion](#)), or inflammatory markers (high C-reactive protein [CRP]
40 levels or low albumin levels) following PEG insertion.

41 **Material and Methods:** The phase angle was assessed from body resistance and reactance
42 as measured by bioelectrical impedance in 131 patients admitted for PEG. Anthropometrics
43 and clinical biochemical measures were collected at the time of PEG insertion, while
44 complications and mortality were assessed at clinical follow-ups. Multivariable logistic
45 regression analysis provided odds ratios (ORs) with 95% confidence intervals (CIs) adjusted
46 for sex, age, body mass index and comorbidity.

47 **Results:** A decreased phase angle did not statistically significantly increase the probability
48 of acute complications or short-term mortality, but predicted increased inflammatory markers
49 (CRP ≥ 10 mg/L (OR 1.63, 95% CI 1.02-2.60), albumin < 30 g/L (OR 2.10, 95% CI 1.24-3.57)
50 and a combination of CRP ≥ 10 mg/L and albumin < 30 g/L (OR 3.06, 95% CI 1.51-6.19)).

51 **Conclusions:** A decreased phase angle did not predict acute complications or short-term
52 mortality after PEG insertion, but predicted increased levels of inflammatory markers.

53 **Keywords:** complications; early mortality; enteral nutrition; malnutrition.

Introduction

Percutaneous endoscopic gastrostomy (PEG) is a procedure undertaken for those in need of nutritional supplementation over a longer or lifelong perspective, e.g. patients with cancer or neurological diseases (1, 2). The insertion of a PEG is usually technically easy, yet the procedure entails a complication rate of about 50% (3). A wide range of complications may occur, including leakage from the stoma in the abdominal wall and deeper situated infections with high risk of mortality. A combination of high C-reactive protein (CRP) and low albumin levels at the time of PEG insertion are markers of more vulnerable patients at a substantial risk of mortality (4). Old age, low body mass index (BMI) and comorbidity are other risk factors for severe complications after PEG insertion (5-7). [Moreover in some situations decisions about inserting a PEG must include serious ethical considerations, e.g., in patients with dementia or in patients who are expected to die within a limited time frame](#) (8, 9)

The phase angle is measured by bioelectrical impedance, which estimates the body composition (10) by measurement of body resistance and reactance to electrical current. While resistance depends on the bodily fluid and electrolyte content, the reactance is produced by cell membranes when storing parts of charge as a capacitor. The phase angle measures the cell membrane function obtained from the relation between resistance and reactance at 50 kHz. The phase angle is a direct and objective parameter without need for data on weight and height (11), which can predict prognosis in a variety of diseases. The aim of the present study was to determine if phase angle predicts acute complications, short-term mortality and increased levels of inflammatory markers (high CRP levels and/or low albumin levels) after insertion of PEG, which could guide the clinical decision-making.

Methods

Study design

This was a prospective cohort study carried out at the Karolinska University Hospital in Stockholm, Sweden. The exposure was phase angle and the outcomes were acute complications, short-term mortality, high CRP levels and low albumin levels. The data collection has been described in detail elsewhere (12). In brief, consecutive patients requiring PEG were prospectively included in the study before PEG insertion. Patients were excluded if they declined, if for any reason it was not possible to perform the bioelectrical impedance spectroscopy measurement, or if the patients had a contraindication for bioelectrical impedance measurement (metal prostheses or cardiac failure). For each patient, clinical and treatment-related data were collected prior to PEG insertion according to a predefined study protocol to ensure completeness and uniformity, and blood samples were drawn before the PEG insertion for analyses of CRP and albumin. Weight was measured using a sitting weighing scale and height by half demi span (measured from the fingertip to the sternal notch using the left arm whenever possible) (13); BMI (kg/m²) was then calculated. All patients routinely fasted for 6 hours before the PEG procedure. The patients were followed up at a specialised clinic after PEG insertion.

Exposure – phase angle

The study exposure was the phase angle value just before the insertion of the PEG. Bioelectrical impedance spectroscopy (BodyScout, Fresenius Kabi) was used to assess the phase angle at 50 kHz. Just before the PEG insertion, the bioelectrical impedance measurement was carried out by a trained nurse or dietitian. The participants were resting in the supine position for at least 5 minutes before the tetrapolar whole body measurement, with electrodes on the dorsal surface of the hand/wrist and the foot/ankle of the same side

according to the manufacturer's instructions. Four electrodes for single use were used. Phase angle was calculated directly from the reactance and resistance. Phase angle is between 5° and 7° in healthy subjects (14). The higher the reactance, the higher the phase angle for any given resistance.

Outcomes

The primary outcomes were acute complications (yes/no) within 14 days of PEG insertion and mortality (yes/no) occurring within 60 days of PEG insertion. Acute complications were defined as peristomal infections, leakage, obstipation and abdominal pain and assessed at follow-up visits at 7 and 14 days post-PEG. Mortality within 60 days was assessed by linkages of personal identity numbers through the Swedish Registry of the Total Population. Secondary outcomes were increased CRP (≥ 10 mg/L), decreased albumin (<30 g/L) or a combination of the two.

Statistical analysis

Multivariable logistic regression analyses were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs). Phase angle was expressed as a linear dependent variable in this model. Adjustments were made for sex (male or female), age (<65 or ≥ 65 years), BMI (<20 or ≥ 20) and comorbidity (cancer or other comorbidity [cardiovascular disease, neurological disease, or diabetes]). All statistical analyses were performed using the statistical software SAS (Statistical Package 9.3; SAS Institute Inc, Cary, NC).

Ethics

Patients, often together with a caregiver or attending relatives, gave informed consent to

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

128 participate in the study. The study was approved by the Regional Ethical Review Board in
129 Stockholm, Sweden.
130

For Peer Review Only

Results

Patients

Among 270 patients receiving a PEG during the study period, 131 (49%) were included in the present study. Non-participation (n=139) was due to technical problems, patients declining participation, or the presence of metal prostheses or cardiac failure. Characteristics of the participants are presented in Table 1. Most patients were male and younger than 65 years and had cancer as the indication for PEG. One third of patients were underweight (BMI <20) at the time of PEG insertion. The median phase angle was 4.8, and was slightly lower in women (4.3) than men (4.8) (Table 1).

Decreased phase angle in relation to outcomes

The results from the multivariable model are presented in Table 2. There were no statistically significant associations between decreased phase angle and risk of complications (OR 0.91, 95% CI 0.59-1.38) or mortality (OR 0.93, 95% CI 0.37-2.37). Decreased phase angle was moderately to strongly associated with increased CRP and decreased albumin levels. A one unit decrease in phase angle was associated with an increased risk of elevated CRP levels (OR 1.63, 95% CI 1.02 -2.60) and low albumin levels (OR 2.10, 95% CI 1.24-3.57), as well as a substantially increased risk of having a combination of increased CRP and decreased albumin (OR 3.06, 95% CI 1.51-6.19).

Discussion

This study indicates that a decreased phase angle at the time for PEG insertion is associated with markers of inflammation - an increase in CRP, decreased albumin as well as both of these outcomes combined, but it did not predict the occurrence of acute complications or mortality within 60 days of PEG insertion.

Strengths of the study include the prospective design, the valid data on the exposure and all outcomes, including objectively measured levels of CRP and albumin. Moreover, changes in phase angle might depend on sex, age, BMI and comorbidity and it was therefore an advantage that these variables were adjusted for in the multivariable model. Weaknesses include potential non-random non-participation, which introduces a risk of selection bias from including more healthy patients. Even though the cohort of 131 subjects is large when comparing with similar studies regarding bioelectrical impedance measurements, the statistical power to assess the outcomes complications and mortality was limited. Thus, the negative findings should be interpreted with caution. Another limitation is that different cut-off values have been used in the literature to assess for phase angle in relation to diagnosis-specific study populations (15). These might not be applicable for populations in a more general clinical situation (16) like for the heterogenic PEG population. To avoid this problem we instead used phase angle as a linear variable. [Moreover, it should be acknowledged that complications might not only be due to the PEG insertion *per se*, but also be caused by metabolic disturbances related to refeeding of malnourished patients \(17\).](#)

Our results showed that a decreased phase angle was associated with a high CRP, a universally accepted indicator of systemic inflammation. Phase angle may be directly affected by a change in electric tissue properties due to the disease itself, inflammation or malnutrition, among others. The strong association between a decrease in phase angle and low albumin

1
2
3 179 levels in the present study might also be due to inflammation, rather than an indicator for
4
5 180 malnutrition (18, 19), as it has historically been described (20). These associations are of
6
7 181 clinical relevance since CRP and albumin levels have been shown to predict mortality
8
9 182 following PEG insertion (5). This finding together with the simplicity and objectivity in the
10
11 183 assessment of the phase angle indicate a potential role in the clinical decision-making in
12
13 184 patients considered for PEG.
14
15
16
17
18
19

20 186 In conclusion, a decreased phase angle reflects increased levels of inflammatory markers -
21 187 CRP, albumin and a combination of the two. These biomarkers indicate worse outcomes
22
23 188 following PEG. However, if the measurement of the phase angle actually facilitates clinical
24
25 189 decision-making for PEG remains uncertain.
26
27
28
29
30
31 192

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

193

194

195

196

197

198

199

200

201

202

203

204

205

206

Acknowledgements

We express our gratitude to all healthcare staff members who cared for the patients receiving a PEG and the management of all documentation, to all the staff involved at the endoscopy unit and to Margrete Gellervik for her valuable administrative help.

Conflict of interest: None declared.

Financial support: The Swedish Cancer Society and through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

References

1. Angus F, Burakoff R. The percutaneous endoscopic gastrostomy tube. medical and ethical issues in placement. *Am J Gastroenterol.* 2003;98(2):272-7.
2. Cullen JJ.
3. Blomberg J, Lagergren J, Martin L, Mattsson F, Lagergren P. Complications after percutaneous endoscopic gastrostomy in a prospective study. *Scand J Gastroenterol.* 2012;47(6):737-42.
4. Blomberg J, Lagergren P, Martin L, Mattsson F, Lagergren J. Albumin and C-reactive protein levels predict short-term mortality after percutaneous endoscopic gastrostomy in a prospective cohort study. *Gastrointest Endosc.* 2011;73(1):29-36.
5. Zopf Y, Maiss J, Konturek P, Rabe C, Hahn EG, Schwab D. Predictive factors of mortality after PEG insertion: guidance for clinical practice. *JPEN J Parenter Enteral Nutr.* 2011;35(1):50-5.
6. Cagin YF, Atayan Y, Erdogan MA, Bilgic Y. Relationship of percutaneous endoscopic gastrostomy-related mortality and morbidity rates and effectiveness with advancing age. *Acta Gastroenterol Belg.* 2015;78(3):292-8.
7. Rimon E, Kagansky N, Levy S. Percutaneous endoscopic gastrostomy; evidence of different prognosis in various patient subgroups. *Age Ageing.* 2005;34(4):353-7.
8. Mitchell SL. CLINICAL PRACTICE. Advanced Dementia. *N Engl J Med.* 2015;372(26):2533-40.
9. Niv Y, Abuksis G. Indications for percutaneous endoscopic gastrostomy insertion: ethical aspects. *Dig Dis.* 2002;20(3-4):253-6.
10. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Gomez JM, et al. Bioelectrical impedance analysis--part I: review of principles and methods. *Clin Nutr.* 2004;23(5):1226-43.
11. Kyle UG, Soundar EP, Genton L, Pichard C. Can phase angle determined by bioelectrical impedance analysis assess nutritional risk? A comparison between healthy and hospitalized subjects. *Clin Nutr.* 2012;31(6):875-81.
12. Blomberg J, Lagergren P, Martin L, Mattsson F, Lagergren J. Novel approach to antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): randomised controlled trial. *BMJ.* 2010;341:c3115. doi: 10.1136/bmj.c3115.
13. Hickson M, Frost G. A comparison of three methods for estimating height in the acutely ill elderly population. *J Hum Nutr Diet.* 2003;16(1):13-20.
14. Bosy-Westphal A, Danielzik S, Dorhofer RP, Later W, Wiese S, Muller MJ. Phase angle from bioelectrical impedance analysis: population reference values by age, sex, and body mass index. *JPEN J Parenter Enteral Nutr.* 2006;30(4):309-16.
15. Norman K, Stobaus N, Zocher D, Bosy-Westphal A, Szramek A, Scheufele R, et al. Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr.* 2010;92(3):612-9.
16. Barbosa-Silva MC, Barros AJ. Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. *Curr Opin Clin Nutr Metab Care.* 2005;8(3):311-7.
17. Judges D, Beverly S, Rio A, Goff LM. Clinical guidelines and enteral nutrition support: a survey of dietetic practice in the United Kingdom. *Eur J Clin Nutr.* 2012;66(1):130-5.
18. Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. *J Am Diet Assoc.* 2004;104(8):1258-64.
19. Jensen GL, Bistrian B, Roubenoff R, Heimbarger DC. Malnutrition syndromes: a conundrum vs continuum. *JPEN J Parenter Enteral Nutr.* 2009;33(6):710-6.

20. Fuhrman MP. The albumin-nutrition connection: separating myth from fact. Nutrition. 2002;18(2):199-200.

Table 1. Characteristics of 131 study patients receiving a percutaneous endoscopic gastrostomy (PEG)

	Number	Per cent
Sex		
Female	46	35
Male	85	65
Age		
<65	75	5
>=65	56	43
Body mass index		
<20	41	31
>=20	90	69
Diagnosis		
Cancer	109	83
No cancer	22	17
Other diagnosis	30	23
No other diagnosis	101	77
Complications within 14 days of PEG		
No	89	68
Yes	42	32
Mortality within 60 days of PEG		
No	124	95
Yes	7	5
CRP level (mg/L)		
<10	78	60
>=10	47	36
missing	6	5
Albumin level (g/L)		
>30	92	70
<30	32	24
missing	7	5
C-reactive protein level >=10 and albumin>=30		
No	99	76
Yes	25	19

missing	7	5
Phase angle median		
Grouped	4.8	
Female	4.3	
Male	4.8	

263

For Peer Review Only

Table 2. Phase angle in relation to outcome variables in study patients receiving a percutaneous endoscopic gastrostomy (PEG)

	Patients Number	Odds ratio*	95% confidence interval
Acute complications			
No	89	1	Reference
Yes	42	0.91	0.59 – 1.38
Mortality within 60 days of PEG			
No	124	1	Reference
Yes	7	0.93	0.37 – 2.37
CRP			
< 10	78	1	Reference
≥10	47	1.63	1.02 – 2.60
Albumin			
≥30	92	1	Reference
< 30	32	2.10	1.24 – 3.57
CRP and albumin			
CRP<10 and albumin ≥ 30	70	1	Reference
CRP≥10 and albumin < 30	25	3.06	1.51 – 6.19

* Adjusted for sex, age, body mass index and comorbidity.