FIZIOLOGIA
physiology

ACCREDITED BY CNCSIS - B+CATEGORY ■ CODE 240

http://www.ebscohost.com/titleLists/a9h-journals.pdf

Fiziologia (Physiology) is issued quarterly
Printed at Editura **EUROSTAMPA**
www.eurostampa.ro
Bd. Revoluţiei din 1989 nr. 26, Timişoara
Tel/fax: 0256-204816
ISSN 1223-2076

Instructions to Authors

Submission: Only original papers in English are considered and should be sent to the following address: carmen.tatu@umft.ro

Manuscripts should be submitted by e-mail only, written in Microsoft Word 97 or later versions.

Conditions: All manuscripts are subject to editorial review. Manuscripts are received with the explicit understanding that they are not under simultaneous consideration by any other publication. Submission of an article for publication implies the transfer of the Copyright from the author the publisher upon acceptance. Accepted papers become the permanent property of "Fiziologia" (Physiology) and may not be reproduced by any means, in-whole or in part, without the written consent of the publisher. It is the author's responsibility to obtain permission to reproduce illustrations, tables, etc. from other publications.

Arrangement:

Title page: The first of each paper should indicate the title, the authors' names and their affiliation(s). A short title for use as running head is also required.

Keywords: for indexing purposes, a list of 3-5 keywords in English and Romanian is essential.

Corresponding author: Indicate the full name, the email address and the phone number.

Abstract: Each paper needs abstract and title in Romanian and English language, fonts size 9, Arial Narrow.

Body text: fonts size 10, Arial Narrow.

Small type: Paragraphs which can or must be set in smaller type (case histories, test methods, etc.) should be indicated with a „p" (petit) in the margin on the left-hand side.

Footnotes: Avoid footnotes. When essential, they are numbered consecutively and typed at the foot of the appropriate page, fonts size 8, Arial Narrow.

Tables and illustrations: Tables (numbered in Roman numerals) and illustrations (numbered in Arabic numerals) should be prepared on separate sheets, fonts size 9, Arial Narrow. Tables require a heading, and figures a legend, also prepared on a separate sheet. For the reproduction of illustrations, only good drawings and original photographs can be accepted; negatives or photocopies cannot be used. When possible, group several illustrations on one block for reproduction (max. size 140x188 mm) or provide crop marks. On the back of each illustration indicate its number, the author's name, and article title.

References: In the text identify references by Arabic figures, (in brackets), fonts size 9, Arial Narrow. Material submitted for publication but not yet accepted should be noted as "unpublished data" and not be included in the reference list. The list of references should include only those publications which are cited in the text. The references should be numbered and arranged alphabetically by the authors' names. The surnames of the authors followed by initials should be given. There should be no punctuation signs other than a comma to separate the authors. When there are more than 3 authors, the names of the 3 only are used, followed by "et al" abbreviate journal names according to the Index Medicus system. (also see International Committee of Medical Journal Editors: Uniform Requirements for manuscripts submitted to biomedical journals. Ann Intern Med 1982; 96: 766-771).

Examples:

(a) Papers published in periodicals: Kauffman HF, van der Heide S, Beaumont F, et al: Class-specific antibody determination against Aspergillus fumigatus by mean of the enzyme-linked immunosorbent assay. III. Comparative study: IgG, IgA, IgM, ELISA titers, precipitating antibodies and IGE biding after fractionation of the antigen. Int Arch Allergy Appl Immunol 1986; 80:300 - 306.

(b) Monographs; Matthews DE, Farewell VT: *Using and Understanding Medical Statistics.* Basel, Karger, 1985.

(c) Edited books: Hardy WD Jr, Essex *M:.FeLV-inducted feline acquired immune deficiency syndrome: A model for human AIDS;* in Klein E(ed): Acquired Immunodeficiency Syndrome. Prag Allergy, Busel, Karger, 1986, vol 37,353 - 376.

Galley proofs: unless indicated otherwise, galley proofs are sent to the first-named author and should be returned with the least possible delay. Alternations made in galley proofs, other than the corrections of printer's errors, are charged to the author. No page proofs are supplied.

CONTENTS

CUPRINS

CHANGES IN SERUM LEPTIN AND ADIPONECTIN LEVELS IN BENINESE PREGNANT WOMEN

BONAVENTURE AWEDE[1], GRACE ADEHAN[2], SOULIATH LAWANI[1], EMMANUEL DOSSOU[1], JUSTIN DENAKPO[3], FRANÇOIS DJROLO[4], MARCELLIN AMOUSSOU-GUENOU[2]

[1]Unité de Physiologie, Faculté des Sciences de la Santé, Université d'Abomey-Calavi
[2]Unité de Biophysique et de Médecine Nucléaire, Faculté des Sciences de la Santé, Université d'Abomey-Calavi
[3]Unité de Gynécologie et d'Obstétrique, Faculté des Sciences de la Santé, Université d'Abomey-Calavi
[4]Unité d'Endocrinologie, Métabolisme et Nutrition, Faculté des Sciences de la Santé, Université d'Abomey-Calavi

ABSTRACT

Background: Adiponectin and leptin plasma levels during normal pregnancy and gestational diabetes mellitus have been studied but there are some variations in the reported results although some trends are observed. In the present study, serum levels of these adipokines have been determined in normal and pregnant women with gestational diabetes mellitus.
Methods: OGTT test has been made in pregnant women for gestational diabetes mellitus screening and in non-pregnant women to assess their glucose tolerance status. Three groups of 12 women were included in the study: non-pregnant women with normal glucose tolerance, pregnant women without and pregnant women with gestational diabetes. Leptin and adiponectin serum levels were then determined by radioimmunoassay at 10-15 weeks and 24-28 weeks of gestational age in normal pregnant women and at 24-28 weeks of gestation in pregnant women with gestational diabetes.
Results: serum leptin level in normal pregnant women at 24-28 weeks of gestation (13.24 ± 3.69 ng/mL) was significantly ($p<0.05$) higher than that in non-pregnant women.
In normal pregnant women, adiponectin levels were 82.83 ± 21.95 µg/mL and 76.31 ± 42.99 µg/mL respectively at 10-15 weeks and 24-28 weeks of gestation and were significantly higher ($p<0.001$) than adiponectin level in non-pregnant women (7.52 ± 4.66 µg/L). Leptin and adiponectin levels in women with gestational diabetes were not significantly different from levels in normal pregnant women.
Conclusion: These data suggest that leptin and adiponectin levels could not systematically be considered as marker of gestational diabetes in all pregnant women population.
Keywords: Leptin, adiponectin, pregnancy, gestational diabetes mellitus

INTRODUCTION

Leptin and adiponectin are two hormones produced by adipose tissue and which are involved in many functions such as reproduction, energy homeostasis and immune system function [1]. In reproductive system, these hormones, especially leptin, modulate sex hormones secretion by acting at different levels of hypothalamic-pituitary-gonadal system [9]. Leptin and adiponectin also modulate tissue insulin sensitivity and high levels of leptin and hypoadiponectinemia have been found associated with insulin resistance [1; 2].

Pregnancy is a physiological condition where insulin resistance occurs, especially, in the second half of pregnancy due to the action of many hormones. Because of this insulin resistance, gestational diabetes mellitus (GDM) is frequently observed during pregnancy [4]. Given their action on energy homeostasis and insulin resistance, the role of leptin and adiponectin during pregnancy has been investigated by many authors. Changes in leptin and adiponectin levels during pregnancy have been described but a great variability was observed in the published data and ethnic differences were also reported [11, 12, 18, 20, 21, 26]. In pregnant women with GDM, compared to normal pregnancy, decreased adiponectin levels have been reported by several authors [3, 5, 28]. Thus, low adiponectin level has been suggested as a marker of GDM. In view of the variability observed from one study to another, it is of great importance to characterize changes in levels of these adipokines during pregnancy in each population. In the present work, we have investigated changes in leptin and

Received 10th of September 2017. Accepted 15th of October 2017. Address for correspondence: Dr Bonaventure AWEDE, Unité de Physiologie, Faculté des Sciences de la Santé, Université d'Abomey-Calavi, 01 BP 188 Cotonou, BENIN; phone: 00229 95 10 43 53; e-mail: Bonawed@yahoo.com

adiponectin levels in normal and pregnant women with GDM from Benin population.

MATERIAL AND METHODS

Subjects

Pregnant women (135) have been recruited in the Gynecology and Obstetrics Clinic of the University Hospital Mother and Child (CHU-MEL) from July 2013 to June 2014. After screening for gestational diabetes mellitus based on an oral glucose tolerance test (OGTT), 12 pregnant women with GDM, 12 pregnant women without GDM were included in the study. Twelve non-pregnant women with normal glucose tolerance served as control. Only subjects who gave a written consent form were included in the study.

Data collection

Anthropometric and clinical data were collected at an antenatal clinic and using a questionnaire. For pregnant women, weight at the first trimester of pregnancy was used to determine the body index mass (BMI).

Oral glucose tolerance test (OGTT)

An OGTT was performed in all pregnant women at 24-28 weeks of gestational age by oral administration of 75g of glucose for the diagnosis of gestational diabetes mellitus. Criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) were used to define GDM [16].

Leptin and adiponectin levels measurement

Blood samples were taken from each subject for measurement of adipokine levels.

Leptin and adiponectin levels were determined at 10-15 weeks and at 24-28 weeks of gestational age in all non-GDM pregnant women. In women with GDM, leptin and adiponectin levels were measured at 24-28 weeks of gestational age because most of them have been recruited after a first trimester of gestation (only three were recruited in the first trimester). Leptin and adiponectin measurement was performed by radioimmunoassay using specific kits purchased from Demeditec Diagnostic (Germany) according to manufacturer instructions.

Statistical analysis

Data are expressed as means ± standard deviation (SD). Means are compared using t-student test. Differences were considered significant for $p<0.05$.

RESULTS

Subjects characteristics

Mean age of all subjects was 27.64 ± 5.92 years. Mean ages of control non-pregnant, normal pregnant and pregnant women with GDM were respectively 24.83 ± 4.22 years, 28.17 ± 4.20 years and 29.92 ± 7.86 years.

Mean BMI of all subjects was 25.85 ± 5.87 kg/m^2 and mean BMI of control non-pregnant, normal pregnant and pregnant women with GDM were respectively 24.09 ± 6.05 kg/m^2 and 26.21 6.09 kg/m^2 and 27.24 ± 5.24 kg/m^2.

Mean blood fasting glucose levels were identical in pregnant and non-pregnant women (0.83 ± 0.12 vs 0.83 ± 0.08) but were significantly higher in women with GDM than in normal pregnant women (0.93 ± 0.12 vs 0.74 ± 0.08; $p<0.001$).

Leptin and adiponectin serum levels in control non-pregnant and in pregnant women without GDM

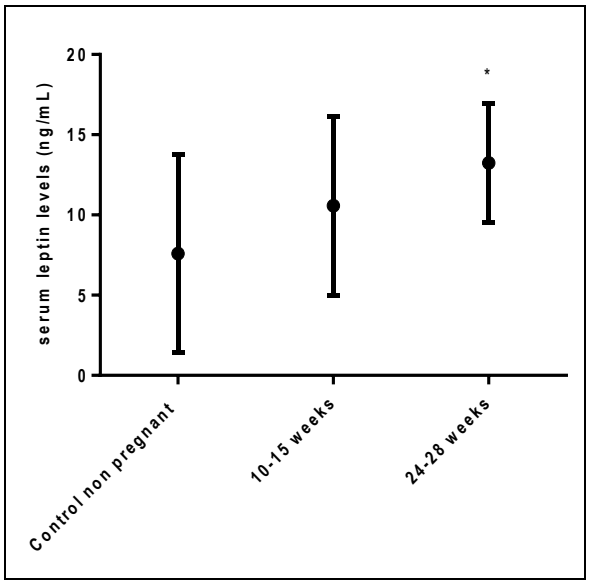

Fig. 1. Serum leptin levels in non-pregnant and pregnant women without gestational diabetes
Values are means ± SD, n = 12 in each group.
*: significant different from control non-pregnant, $p<0.05$.

Figure 1 shows mean serum leptin levels control non-pregnant and in pregnant women without GDM.

In normal pregnant women mean leptin levels were 10.58 ± 5.57ng/mL and 13.24 ± 3.69 ng/mL at respectively 10-15 weeks and 24-28 weeks of gestation. Mean leptin level at 24-28 weeks was significantly higher ($p<0.05$) than leptin level in non-pregnant women (7.60 ± 6.2 ng/mL) but was not different from leptin level at 10-15 weeks of gestation.

Levels of adiponectin is represented in figure 2. Adiponectin levels were 82.83 ± 21.95 µg/mL and 76.31 ± 42.99 µg/mL in normal pregnant women respectively at 10-15 weeks and 24-28 weeks of gestational age. These adiponectin levels were significantly higher ($p<0.001$) than that in non-pregnant women (7.52 ± 4.66 µg/L). There was

no significant difference between adiponectin levels at 10-15 weeks and at 24-28 weeks.

Leptin and adiponectin levels in pregnant women with GDM

Serum leptin level at gestational age of 24-28 weeks was 14.84 ± 8.45 ng/L in pregnant women with GDM. This leptin level was significantly higher ($p<0.05$) than leptin level in control non-pregnant women but was not different from leptin level in normal pregnant women.

Adiponectin mean level at 24-28 weeks of gestation was 110.86 ± 50.99 µg/L. This adiponectin level was significantly higher ($p<0.001$) than adiponectin level in control non-pregnant women but was not different from adiponectin level in normal pregnant women.

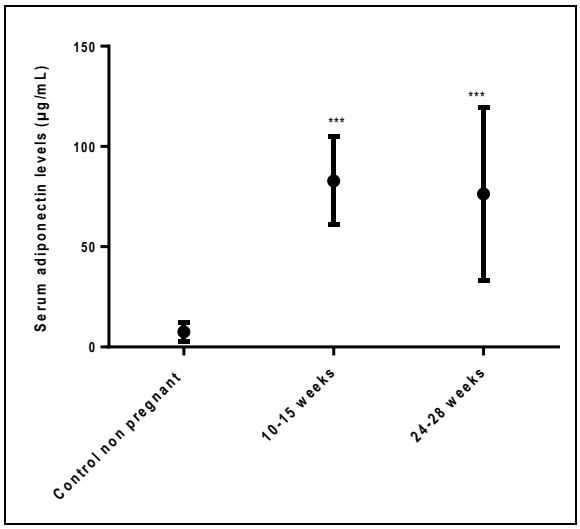

Fig. 2. Serum adiponectin levels in non-pregnant and pregnant women without gestational diabetes
Values are means ± SD, n = 12 in each group.
***: significant different from control non-pregnant, $p<0.001$.

DISCUSSION

The main findings of the present study were that in pregnant women, compared to non-pregnant women, there were increased levels of both serum leptin and adiponectin levels and that serum leptin and adiponectin levels in women with GDM and in women without GDM were not significantly different at 24-28 weeks of gestation.

As found in our study, increased leptin levels during pregnancy have been reported by several studies [2, 14, 21, 27]. Although many authors found an early significant increase in leptin levels, in our study, leptin levels in the first trimester of pregnancy were not significantly different from non-pregnant control levels. Many mechanisms including increase maternal production and placental production of leptin are thought to be involved in this rise of leptin levels during pregnancy [6].

Leptin level in women with GDM was not significantly different from that in normal pregnant women. Our results are in agreement with many published data [2, 15, 20, 25]. However, increased leptin levels in women with GDM, compared to normal pregnant women, has also been reported [5, 11, 13]. Early significant increased leptin levels in pregnant women who developed latter GDM have been reported and thus increased leptin level has been suggested as early marker of GDM [11, 24]. Further studies which will investigate early changes in leptin levels should be performed on large size of our population before making such a conclusion.

Increased adiponectin levels during normal pregnancy was observed in our study. In published data, variable profiles of adiponectin level have been described. In most studies, compared to non-pregnant women, adiponectin levels in pregnant women were not significantly different, during the first trimester [7, 10, 12]. After the first trimester, either no change, a trend to a decrease or significant decrease in adiponectin levels have been reported [7, 10, 18, 23]. However, increased adiponectin level during pregnancy, as we found in our study, has also been described. Fuglsang and co-workers found an increased level of adiponectin at 17 weeks of pregnancy before its decline later during pregnancy [12]. In addition, although adiponectin level in all pregnant women of their study was not significantly different from that of non-pregnant women, Nien and co-worker found that adiponectin levels in pregnant women with a BMI less than 25 were higher than that of non-pregnant women [22]. In our study, compared to non-pregnant women, a more than ten-times increased in adiponectin level (which persisted until 24-28 weeks) was already observed at 10-15 weeks in normal pregnant women. This is the first time a dramatic increase in adiponectin levels is described in normal pregnant women. As pregnancy is a physiological condition where tissue insulin resistance occurs and as adiponectin is a hormone which increases insulin sensitivity, this increase in adiponectin levels in women with normal glucose tolerance could be a mechanism which prevents or limits insulin resistance during pregnancy.

In our study, adiponectin levels, measured at 24-28 weeks in women with GDM, were not significantly different from those in women without GDM. Our data are in agreement with a previous work which reported, in the second trimester, no significant difference in adiponectin levels between GDM and normal pregnant women although a significant decrease in adiponectin levels was observed in GDM women in the third trimester [23]. In contrast to our results, in almost all other studies, adiponectin levels have been shown to be lower in women with GDM than in women without GDM [5, 13, 19, 25, 28]. Low levels of adiponectin were also already observed early in pregnancy before the development of GDM and adiponectin has been suggested as a marker of GDM [17, 28]. Our results suggest however that decreased adiponectin levels could not be systematically

observed in all women with GDM. Ethnic specificity could be involved in the regulation mechanisms of adiponectin in pregnant women as ethnic differences in adiponectin levels during pregnancy have been described [8, 26].

In the present study, changes in leptin and adiponectin levels in women with GDM in were investigated only at 24-28 weeks of gestation. Longitudinal study should be performed throughout the pregnancy and in the post-partum to allow a best assessment of leptin and adiponectin changes during pregnancy. Another limit of our study is the small size of our study population. Further studies should be conducted on large population to confirm the findings of the present work.

REFERENCES

1. Ahima RS. Adipose tissue as an endocrine organ. *Obesity* 2006; 14: 242S-49S.
2. Al-Atawi FS, Warsy AS, Babay ZA et al. Leptin concentration during different stages of pregnancy. *Clin Exp Obstet Gynecol* 2004; 31 (3): 211-6.
3. Altinova AE, Toruner F, Bozkurt N et al. Circulating concentrations of adiponectin and tumor necrosis factor-alpha in gestational diabetes mellitus. *Gynecol Endocrinol* 2007; 23 (3): 161-5.
4. American Diabetes Association. Gestational diabetes mellitus. *Diabetes Care* 2003; 26: S103-S105.
5. Boyadzhieva M, Atanasova I, Zacharieva S et al. Adipocytokines during pregnancy and postpartum in women with gestational diabetes and healthy controls. *J Endocrinol Invest* 2013; 36 (11): 944-9.
6. Briffa JF, McAinch AJ, Romano T et al. Leptin in pregnancy and development: a contributor to adulthood disease? *Am J Endocrinol Metab* 2015; 308: E335–E350.
7. Cesh K, Baranyl E, Melczer Z. Plasma adiponectin and pregnancy-induced insulin resistance. *Diabetes Care* 2004, 27 (1): 274
8. Chen X, Scholl TO. Ethnic differences in maternal adipokines during normal pregnancy. *Int J Environ Res Public Health* 2016, 13: 8.
9. Chou SH, Mantzoros C. Role of leptin in human reproductive disorders. J Endocrinol 2014; 223: T49-T62.
10. Elshoreya H, Steinberg F, Perry R. Serum adiponectin levels are significantly reduced during the second half of normal pregnancy. *Clin Exp Obstet Gynecol* 2011; 38 (3): 211-3.
11. Fatima SS, Alam F, Chaudhry B et al. Elevated levels of chemerin, leptin and interleukin-18 in gestational diabetes mellitus. *J Matern Fetal Neonatal Med* 2017; 30 (9): 1023-28.
12. Fuglsang J, Skjaerbaek C, Frystyk J et al. A longitudinal study of serum adiponectin during normal pregnancy. *BJOG* 2006; 113: 110-113.
13. Gao XL, Yang HX, Zhao Y. Variation of tumor necrosis factor-alpha, leptin and adiponectin in mid-trimester of gestational diabetes mellitus. *Chin Med J* 2008; 121 (8): 701-5.
14. Highman TJ, Friedman JE, Huston LP et al. Longitudinal changes in maternal serum leptin concentrations, body composition and resting metabolic rate in pregnancy. *Am J Obstet Gynecol* 1998; 178 (5): 1010-5.
15. Horosz E, Bomba-Opom DA, Szymanska M et al. Third trimester plasma adiponectin and leptin in gestational diabetes and normal pregnancies. *Diabetes Res Clin Pract* 2011; 93 (3): 350-6.
16. IADPSGCP. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care* 2010; 33 (3): 676-82.
17. Lain KY, Daftary AR, Ness RB et al. First trimester adipocytokine concentrations and risk of developing gestational diabetes later in pregnancy. *Clin Endocrinol* 2008; 69 (3): 407-11.
18. Mazaki-Tovi S, Kanety H, Pariente C et al. maternal serum adiponectin levels during human pregnancy. *J Perinat* 2007; 77-81.
19. Mohammadi T, Paknahad Z. adiponectin concentration in gestational diabetic women: a case-control study. *Clin Nutr Res* 2017; 6 (4): 267-276.
20. Mokhtari M, Hashemi M, Yaghmaei M et al. Evaluation of the serum leptin in normal pregnancy and gestational diabetes mellitus in Zahedan, southeast Iran. *Arh Gynecol Obstet* 2011, 284 (3): 539-42.
21. Mukherjea R, Castonguay TW, Douglass LW et al. Elevated leptin concentrations in pregnancy and lactation: possible role as a modulator of substrate utilization. *Life Sci* 1999; 65 (11): 1183-93.
22. Nien JK, Makaki-Tovi S, Romero R et al. Plasma adiponectin concentration in non-pregnant, normal and overweight pregnant women. *J Perinat Med* 2007; 35: 522-31.
23. Noureldeen AFH, Qusti SY, Al-seeni MN et al. Maternal leptin, adiponectin, resistin, visfatin and tumor necrosis factor-alpha in normal and gestational diabetes. *Ind J Clin Biochem* 2014; 29 (4): 462-70.
24. Qiu C, Williams MA, Vadachkoria S et al. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. *Obstet Gynecol* 2004; 103 (3): 519-25
25. Ranheim T, Haugen F, Staff AC et al. adiponectin is reduced in gestational diabetes mellitus in normal weight women. *Acta Obstet Gynecol Scand* 2004; 83 (4): 341-7.
26. Retnakaran R, Hanley AJ, Raif N et al. hypoadiponectinaemia in south Asian women during pregnancy: evidence of ethnic variation in adiponectin concentration. *Diabet Med* 2004; 21 (4): 388-92.
27. Rump P, Otto SJ, Hornstra. Leptin and phospholipid-esterified docohexaenoic acid concentrations in plasma of women: observation during pregnancy and lactation. *Eur J Clin Nut* 2001; 55: 244-51.
28. Thagaard IN, Krebs L, Holm JC et al. Adiponectin and leptin as first trimester markers for gestational diabetes mellitus: a cohort study. *Clin Chem Lab Med* 2017; 55 (11): 1805-1812.
29. Yadav A, Kataria MA, Saini V et al. Role of leptin and adiponectin in insulin resistance. *Clin Chim Acta* 2013; 417: 80-4.

COMPLICATIONS OF EXTREME PREMATURITY

IACOB DANIELA[1], DIMA MIRABELA[1], NYIREDI ALEXANDRA[2], IACOB RADU EMIL[2]

[1]Victor Babes University of Medicine and Pharmacy Timisoara, Neonatology Department
[2]Victor Babes University of Medicine and Pharmacy Timisoara, Pediatric Surgery Department

ABSTRACT

Extremely low birth weight newborns are exposed to developing a large spectrum of complications, which are responsible for increased mortality rates in this group of preterm infants. We aimed to analyse the perinatal complications of extreme prematurity that cause high rates of infant morbidity and mortality. We have included 46 extreme low birth weight infants admitted to the Neonatal Intensive Care Unit of Bega Maternity Hospital Timisoara, Romania in the period of 01.01.2012 - 31.12.2013, mean birth weight was 859.35+/-153g. The major causes of mortality were sepsis (46%), perinatal asphyxia (20%) and pulmonary hemorrhage (19%). Respiratory distress syndrome, perinatal hypoxic-ischemic encephalopathy, cerebral hemorrhage, cardiopulmonary arrest, anemia of prematurity and of other causes, acute renal failure and infections were among the most common complications in our group. We have found that complications of prematurity are inversely proportional to birth weight and gestational age and are correlated with morbidity and mortality rates among ELBW preterm infants.

INTRODUCTION

Fifteen million preterm infants (gestational age [GA] <259 days or <37 weeks) are born each year around the world, and the incidence of prematurity is 5 – 18% [1-2]. The extremely low birth weight (ELBW) infant is weighing under 1,000g at birth. Complications of extreme prematurity, associated with neonatal adjustment disorders and responsible for increased mortality rates, are: respiratory, neurologic, cardiovascular, hematologic, metabolic, renal, gastrointestinal, thermoregulation, immunologic, ophthalmologic and hearing disorders etc. [3-7]. This study aimed to analyze the perinatal complications of extreme prematurity, leading to increased infant morbidity and mortality risks for extremely low birth weight babies.

MATERIAL AND METHOD

The study group comprises 46 ELBW newborns, birth weight (BW) <1,000g, admitted to the Neonatal Intensive Care Unit of Bega Maternity Hospital Timisoara, Romania in the period of 01.01.2012 - 31.12.2013. This is a transversal (retrospective observational) study. Inclusion criteria: preterm infants born alive during 2012 and 2013 years in the Bega Maternity Hospital, birth weight under 1,000 g, GA under 30 weeks. Exclusion criterion: ELBW infants born dead.

Statistical analysis

Data extracted from clinical observation sheets of preterm babies were processed and analyzed using the SPSS statistical programme version 20.0. We have used 95% confidence interval and 5% significance level.

RESULTS

The study group comprises 46 ELBW infants, treated in the Neonatal Intensive Care Unit of Bega Maternity Hospital Timisoara within two years. The gender distribution of ELBW preterm infants was as follows: 52.1% girls and 47.9% boys; the female gender prevails both in number and survival rate: 60.7% girls, compared with 39.3% boys. The mode of delivery was vaginal in 39.1% and caesarean section in 60.9% of the cases. The mean birth weight was 859.35+/-153g (<1,000g; lowest BW=400g), with the mean gestational age of 26.65+/-1 week (23 - 29 weeks). Survival rate of ELBW preterm babies in the study group was 60.9% (Figure 1).

Received 10th of October 2017. Accepted 2nd of November 2017. Address for correspondence: Daniela Iacob, Department of Neonatology, "Victor Babeș" University of Medicine and Pharmacy Timișoara, Eftimie Murgu Square No. 2A, RO-300041, Timișoara, Romania; e-mail: danielariacob@yahoo.com

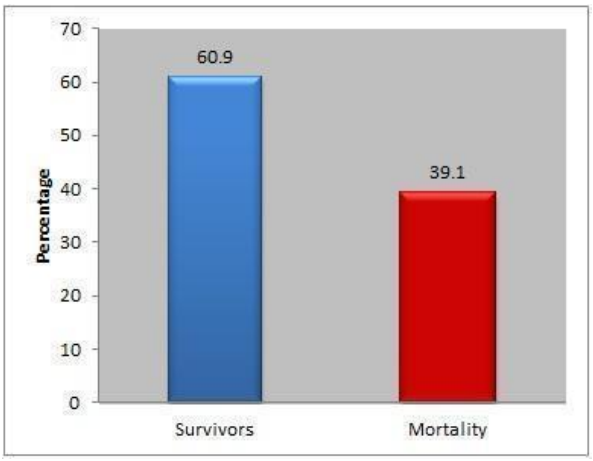

Fig. 1. Survival rate of ELBW preterm babies in the 2012-2013 period

Mortality rate of ELBW preterm babies varied by gender: 38.9% girls and 61.1% boys (Figure 2).

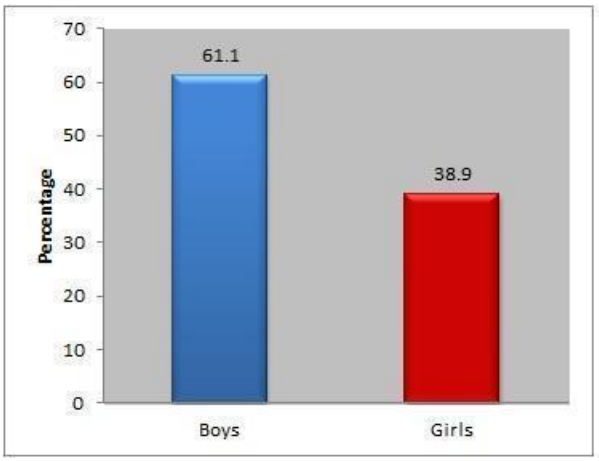

Fig. 2. Mortality rate of ELBW preterm babies in the 2012-2013 period

Respiratory complications:

Respiratory distress syndrome (RDS) was seen in 91.3% of the patients in this study and apnea in 17.4%. Both RDS and apnea of prematurity were seen in 19% of the preterm babies. Pneumothorax was a complication seen in 13%, while pulmonary hemorrhage was present in 17.4% of the ELBW preterm infants. Bronchopneumonia occurred in 15.2%, and chronic lung disease in 4.3% of the cases. We found statistically significant differences between percentages in the group of infants with RDS and respiratory failure, and those without RDS who developed respiratory failure ($p<0.005$). No significant differences were found between percentages in the group of preterm babies with apnea and respiratory failure, and the group of preterm infants without apnea who developed respiratory failure ($p>0.05$).

Neurologic complications:

Perinatal hypoxic-ischemic encephalopathy (HIE), diagnosed by the means of transfontanellar ultrasound, occurred in a large number of ELBW preterms, as follows: mild, 50% (57.6% survivors), moderate, 6.5% (100% survivors) and severe, 41.3% (63.6% survivors). Cerebral hemorrhage (moderate and severe intraventricular hemorrhage), diagnosed by ultrasound, was seen in 52.1% of the cases. Periventricular leukomalacia was diagnosed in 4.3%, and porencephaly in 2.1% of the cases.

Cardiovascular complications:

21.7% of the patients enrolled in the study have had patent ductus arteriosus (PDA) and 52.2% developed cardiopulmonary arrest. No significant differences have been found between percentages of deceased preterm infants with and without PDA ($p=0.9$). A 0.58 correlation was found between respiratory and cardiovascular complications ($p=0.01$).

Hematologic complications were mainly represented by anemia of prematurity and of other causes, which was seen in 50% of the ELBW preterm infants: 78.2% survived and 27.8% died.

Metabolic complications were seen in 76% of the preterm infants included in the study, which had neonatal hypo-/hyperglycemia, hypocalcemia, hyperkalemia and disorders in protein metabolism.

Gastrointestinal complications were diagnosed in 47.8% of the ELBW preterm babies.

Renal complications were represented by acute renal failure in 39.5% of cases, out of which 23.5% survived and 72.5% died.

Immunologic complications: There was a 0.3 correlation between premature rupture of membranes and fetal-maternal infection ($p= 0.04$, $OR=3.5$).

Ophthalmologic complications: A 0.5 correlation between HIE and retinopathy of prematurity (ROP) ($p<0.001$) was found. All preterm babies with retinopathy also had HIE, accounting for 17.39% of the newborns included in this study.

The death variable is explained by the aid of the following variables: APGAR score and respiratory failure, with 40% proportion invasion.

When generating the ROC curve for respiratory failure and deaths among ELBW preterms, we have obtained a 0.79 area ($p=0.001$); this proved to be a good model, with 72% sensitivity.

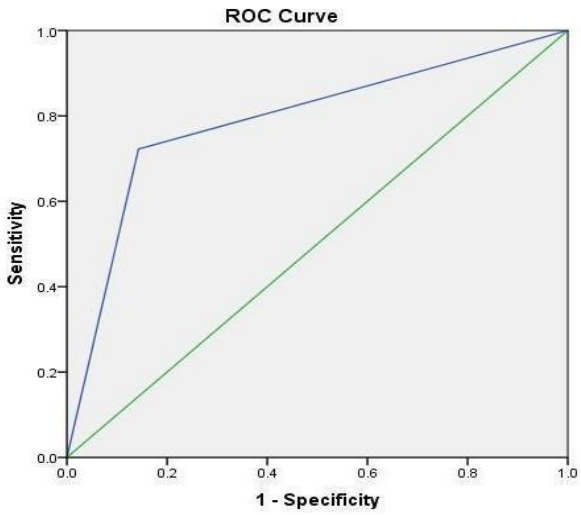

Fig 3. ROC curve for respiratory failure and deaths

DISCUSSIONS

Our study intended to show the complications of prematurity among extremely low birth weight newborns (BW<1000g) treated in the Neonatal Intensive Care Unit of Bega Maternity Hospital Timisoara, Romania; complications of prematurity are inversely proportional to birth weight and gestational age and determine morbidity and mortality rates among ELBW preterm newborns.

Results of researches on the survival rate among ELBW newborns vary according to the countries where studies [6,8,10,12,23] were performed (from 52% to 56%). In our group, we have calculated a 60.9% survival rate, with better outcomes for female newborns. The major causes of mortality were sepsis (46%), perinatal asphyxia (20%) and pulmonary hemorrhage (19%). The most frequent respiratory complications were: RDS, apnea of prematurity, pulmonary hemorrhage, pneumothorax, and chronic lung disease. Antenatal corticosteroids given to mothers at risk of premature delivery (<34 weeks pregnancy), decreases RDS incidence to 50%, with significant impact on mortality reduction [8,14,18]. Antenatal corticosteroids, surfactant therapy, non-invasive respiratory support, prevention of infections and optimal nutritional support for ELBW infants increase their survival rate both on the short and long run [13,14,18]. In our study, antenatal corticosteroids were used in 23.9% of the ELBW preterms with respiratory distress syndrome. RDS was found in 91.3% of the ELBW newborns in our study group.

Neurologic complications are a hallmark of extreme prematurity. Intracranial hemorrhage (intraventricular hemorrhage-IVH, subdural hemorrhage, subarachnoid hemorrhage and intraparenchymal hemorrhage) are often seen in ELBW preterm infants [25-27]. IVH incidence is 16 - 65%; in 22.5% of the cases, IVH was the cause of death [8,26]. Moderate and severe HIE (47.8%), as well as moderate and severe intraventricular hemorrhage (52.2%) were the main neurologic complications in the ELBW newborns in this study.

As cardiovascular complications concerns, PDA was seen in 21.7% of the cases in our clinic.

The hematologic complications in this study were anemia and hyperbilirubinemia. Hyperbilirubinemia was encountered in 59.8% of the cases. Anemia of prematurity and of other causes was seen in 50% of the newborns in the study.

Metabolic complications (hypo-/hyperglycemia, disorders in calcium metabolism): approximately 53% of the ELBW preterm babies with metabolic disorders die perinatally or have neurologic sequelae [29-31]. In our study, this type of complications represent 76% of the cases.

Renal complications, such as acute renal failure (ARF) and fluid and electrolyte imbalances, increase mortality rates among ELBW preterm infants. ARF was seen in 39.5% of the preterm newborns in the study group.

The gastrointestinal complications of prematurity are necrotizing enterocolitis (NEC), diarrheal disease and feeding disorders. In our study, 47.8% of the newborns had gastrointestinal disorders.

The main ophthalmologic complications of extreme prematurity are retinopathy of prematurity and retinal detachment, complicated with vision loss or blinding. Incidence of blindness caused by ROP is 2 - 9% in ELBW newborns with high risk of ROP [37]. ROP was diagnosed in 17.3% of the cases (n=8). In this study, all the preterm infants who had ROP also had HIE, as shown by ultrasound.

CONCLUSIONS

Extremely premature newborns are at increased risk of complications and death. Respiratory, neurologic, cardiovascular, hematologic, metabolic, gastrointestinal, renal complications, immunologic and ophthalmologic complications were seen in the study group. Complications of prematurity are inversely proportional to birth weight and gestational age and are correlated with morbidity and mortality rates among ELBW preterm infants. Extremely low birth weight, mechanical ventilation and hypotensive shock are predictors of morbidity. Antenatal corticosteroids, surfactant therapy, non-invasive respiratory support, prevention of infections and optimal nutritional support for ELBW infants increase their survival rate.

REFERENCES

1. Mandy G. Incidence and mortality of the premature infant. UpToDate. 2014 Dec. http://www.uptodate.com/contents/incidence-and-mortality-of-the-premature-infant

2. Blencowe H, Cousens S, Chou D, Oestergaard, Say L, Moller A-B, Kinney M, Lawn J. Born too soon: the global epidemiology of 15 million preterm births. *Reproductive Health.* 2013; 10 (Suppl 1):S2.
3. Whiteman VE, August EM, Mogos M, Naik M, Garba M, Sanchez E, Weldeselasse HE, Salihu HM. Preterm birth in the first pregnancy and risk of neonatal death in the second pregnancy: A propensity score-weighted matching approach. *Journal of Obstetrics and Gynaecology*. 2015; 35(1):30-36.
4. Jacob J, Kamitsuka M, Reese C, Kelleher A, Spitzer A. Etiologies of NICU Death. *Pediatrics.* 2015; 135(1):59-65.
5. Mukhopadhyay K, Louis D, Mahajan G, Mahajan R. Longitudinal growth and post-discharge mortality and morbidity among extremely low birth weight neonates. *Indian Pediatrics.* 2014; 51(9):723-726.
6. Mukhopadhyay K, Louis D, Mahajan R, Kumar P. Predictors of mortality and major morbidities in extremely low birth weight neonates. *Indian Pediatrics.* 2013; 50(12):1119-1123.
7. Mari G, Dhanireddy R. 155: Ten year very low birth weight infant mortality/morbidity trends at a regional perinatal center: effect of perinatal and neonatal quality improvement program. *American Journal of Obstetrics and Gynecology.* 2015;212(1)Supplement:s94.
8. Tagare A, Chaudhari S, Kadam S, Vaidya U, Pandit U, Sayyad MG. Mortality and morbidity in extremely low birth weight (ELBW) infants in a neonatal intensive care unit. *Indian J Pediatr.* 2013; 80(1):16-20.
9. Markestad T, Kaaresen PI, Ronnenstad A, Reigstad H, Lossius K, Medbo S, Zanussi G, Engelung IE, Polit C, Skjaerven R, Irgens L.Early death, morbidity and need of treatment among extremely premature infants. *Pediatrics.* 2005; 115(5):1289-1298.
10. Ogawa M, Matsuda Y, Kanda E, Konno J, Mitani M, Makino Y, Matsui H. Survival rate of extremely low birth weight infants and its risk factors: case-control study in Japan. *ISRN Obstetrics and Gynecology.* 2013; article ID873563.
11. Abrams S, Schanler R, Lee M, Rechtman D. Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeeding medicine.* 2014; 9(6):281-286.
12. Su B-H, Hsieh W-H, Hsu C-H, Chang J-H, Lien R, Lin C-H. Neonatal outcomes of extremely preterm infants from Taiwan: comparation with Canada, Japan, and the USA. *Pediatrics and Neonatology*. 2014;55(6),419-498.
13. Crowther C, Aghajafari F, Askie L, Asztalos E, Brocklehurst P, Bubner T, Doyle L, Dutta S, Garite T, Guinn D, Hallman M, Hannah M, Hardy P, Maurel K, Mazumder P, McEvoy C, Middleton P, Murphy K, Peltoniemi O, Peters D, Sullivan L, Thom E, Voysey M, Wapner R, Yelland L, Zhang S. Repeat prenatal corticosteroid prior to preterm birth: a systematic review and individual participant data meta-analysis for the PRECISE study group (prenatal repeat corticosteroid international IPD study group: assessing the effects using the best level of evidence) study protocol. *Systematic Reviews.* 2012; 1:12.
14. Martin R, Fanaroff A. The preterm lung and airway: past, present, and future. *Pediatrics and Neonatology*. 2013; 54(4):228-234.
15. Soll R, Suresh G, Willson D, Egan E, Notter R. Surfactant. Pediatric and neonathal mechanical ventilation. *Springer.* 2014;761-807.
16. Iyengar A, Davis JM. Drug therapy for the prevention and treatment of bronchopulmonary dysplasia. *Frontiers in pharmacology: Obstetric and pediatric pharmacology.* 2015; 6:12.
17. Grasso C, Sciacca P, Giacchi V, Carpinato C, Mattia C, Palano MG, Betta P. Effects of sustained lung inflation,a lung recruitment maneuver in primary acute respiratory and cerebral outcomes in preterm infants. *Early Human Development.* 2015; 91(1):71-75.
18. Zhang R, Zhang K, Yuan L, Wang J, Chen C, Shi W. Clinical analyses of 105 extremely low birth weight infants. Zhonghua Yi Xue Za Zhi. 2014; 94(6):446-448.
19. Bohn D, Dargaville P, Davis P, Hutchison A, Owen L. Acute neonatal respiratory failure. Pediatric and Neonatal Mechanical Ventilation. *Springer*. 2014; 1185-1265.
20. Smolarova S, Kocvarova L, Matasova K, Zibolen M, Calkovska A. Impact of Updated European Consensus Guidelines on the Management of Neonatal Respiratory Distress Syndrome on Clinical Outcome of Preterm Infants. *Advs Exp.Medicine,Biology-Neuroscience and Respiration.* 2015; 4:61-66.
21. Ronkainen E, Dunder T, Peltoniemi O, Kaukola T, Marttila R, Hallman M. New BPD predicts lung function at school age: Follow-up study and meta-analysis. *Pediatric Pulmonology.* 2015.
22. Yum SK, Moon C-J, Youn Y-A, Lee HS, Kim A-Y. Risk factor profile of massive pulmonary haemorrhage in neonates: the impact on survival studied in a tertiary care centre. *The Journal of Maternal-Fetal&Neonatal Medicine.* 2015.
23. Finer N, Higgins R, Kattwinkel J, Martin R. Summary proceedings from the apnea-of-prematurity group. *Pediatrics.* 2006; 117(1):47-51.
24. Wei Y-H, Lei C-H, Cheng H-N, Tsao L-T, Hsiao C-C. Pigtail catheters versus traditional chest tubes for pneumothoraces in premature infants treated in a neonatal intensive care unit. *Pediatrics and Neonatal Intensive Care Unit.* 2014;55(5): 376-380.
25. Davis AS, Hintz S, Goldstein R, Ambalavanan N, Bann C, Stoll B, Bell EF, Shankaran S, Laptook A, Walsh M, Hale E, Newman N, Das A, Higgins R. Outcomes of extremely preterm infants following severe intracranial hemorrhage. *J Perinatol.*2014; 34(3):203-208.
26. Ritivoiu ME, Brezan FN, Cristea C, Codreanu I, Goran D, Ghita L, Anca IA. Pery-intraventricular hemorrhage in preterm infants: the importance of screening by transfontanellar ultrasound. *Revista Romana de Pediatrie.* 2013; 62(4):382-440.

27. Hintz S, Barnes P, Bulas D, Slovis T, Finer N, Wrage L, Das A, Tyson J, Stevenson D, Carlo W, Walsh M, Laptook A, Yoder B, Van Meurs K, Faix R, Rich W, Newman N, Cheng N, Heyne R, Vohr B, Acarregui M, Vaucher Y, Pappas A, Peralta-Carcelen M, Wilson-Costello D, Evans P, Goldstein R, Myers G, Poindexter B, McGowan E, Adams-Chapman I, Fuller J, Higgins R. Neuroimaging and neurodevelopmental outcome in extremely preterm infants. *Pediatrics.* 2015; 135(1):32-42.
28. Rolland A, Shankar-Aguilera S, Diomande D, Zupan-Simunek V, Boileau P. Natural evolution of patent ductus arteriosus in the extremely preterm infant. *Arch Dis Child Fetal Neonatal Ed.* 2015;100(1):55-58.
29. Logan W, O'Shea TM, Allred E, Laughon M, Bose C, Dammann O, Batton D, Engelke S, Leviton A. Early postnatal hypotension and developemental delay at 24 months of age among extremely low gestational age newborns. *Arch Dis Child Fetal Neonatal Ed.* 2011; 96:321-328.
30. Benli AR, Benli NC, Usta AT, Atakul T, Koroglu M. Effect of maternal age on pregnancy outcome and cesarean delivery rate. *J Clin Med Res.* 2015;7(2):97-102.
31. Randolph DA, Nolen TL, Ambalavanan N, Carlo WA, Peralta-Carcelen M, Das A, Bell EF, Davis AS, Laptook AR, Stoll BJ, Shankaran S, Higgins R. Outcomes of extremely low birthweight infants with acidosis at birth. *Arch Dis Child Fetal Neonatal Ed.* 2014;99(4):263-8.
32. Ou X, Glasier CM, Ramakrihnaiah RH, Mulkei SB, Ding Z, Angtuaco TL, Andres A, Kaiser JR. Impaired white matter developement in extremely- low-birth-weight infants with previous brain hemorrhage. *Am J Neuroradiol* 2014;35:1983-1989.
33. Oza S, Lawn J, Hogan D, Mathers C, Cousens S. Neonatal cause-of-death estimates for the early and late neonatal periods for 194 countries: 2000-2013. *Bull World Health Organ.* 2015; 93:19-28.
34. Abrahamsson T, Rautava S, Moore A, Neu J, Sherman P. The time for a confirmative necrotizing enterocolitis probiotics preventions trial in the extremely low birth weight infant in North America is now. *The Journal of Pediatrics.* 2014; 165(2):389-394.
35. Bancardi E, Claure N. Chronic respiratory failure in neonates. Pediatric and Neonatal Mechanical *Ventilation.* 2015. Ed.Springer, 1267-1277.
36. Autmizguine J, Hornik C, Benjamin D, Laughon M, Clark R, Cotten M, Cohen-Wolkowiez M, Benjamin D, Smith B. Anaerobic antimicrobial therapy after necrotizing enterocolitis in VLBW infants. *Pediatrics.* 2015;135(1):117-125.
37. Kennedy KA, Wrage LA, Higgins RD, Finer NN, Carlo WA, Walsh MC, Laptook AR, Faix RG, Yoder BA, Schibler K, Gantz MG, A Das, Newman NS, Phelps DL. Evaluating retinopathy of prematurity screening guidelines for 24-to 27-week gestational age infants. *Journal of Perinatology*. 2014;34:311-318.

COMPLICAȚIILE PREMATURITĂȚII EXTREME

REZUMAT

Nou-născuții cu greutate extrem de mică la naștere sunt expuși unui spectru larg de complicații, care determină o rată crescută a mortalității în acest grup de prematuri. Scopul nostru a fost să analizăm complicațiile prematurității extreme, care duc la rate mari de morbiditate și mortalitate infantilă. Am inclus în studiu 46 de prematuri cu greutate extrem de mică la naștere internați în Secția Neonatologie și Terapie Intensivă a Maternității Bega Timișoara, România în perioada 01.01.2012 - 31.12.2013, cu o greutate medie la naștere de 859,35+/-153g. Cauzele majore de deces au fost sepsisul (46%), asfixia perinatală (20%) și hemoragia pulmonară (19%). Sindromul de detresă respiratorie, encefalopatia hipoxic ischemică perinatală, hemoragia cerebrală, stopul cardio-respirator, anemia prematurității și de alte cauze, insuficiența renală acută și infecțiile au fost unele dintre cele mai frecvente complicații în grupul de studiu. În urma acestui studiu am constatat o relație invers proporțională între complicațiile prematurității, pe de o parte, și greutatea la naștere și vârsta gestațională, pe de altă parte, acestea corelându-se cu ratele morbidității și mortalității în rândul prematurilor cu greutate extrem de mică la naștere.

RELAPSED PSEUDOMYXOMA PERITONEI. A CASE REPORT

RAMONA CIOBOATA[1], MARIUS GEORGESCU[2], ALICE ELENE GAMAN[3]

[1] Internal Medicine-Pulmonology Department, University of Medicine and Pharmacy Craiova, Romania
[2] Physiology Department, University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania
[3] Microbiology Department, University of Medicine and Pharmacy of Craiova, Romania

ABSTRACT

Pseudomyxoma peritonei (PMP) constitutes a rare, chronic, relapsing pathological entity with an estimated incidence of 1-2 cases per 10000 laparoscopies (1 case / million / year) characterized by the accumulation of relatively mucous semi-solid masses in the peritoneal cavity.

Pseudomyxoma peritonei presents a wide spectrum of manifestations, ranging from benign to borderline to malignant.

We present the case of a 49-year-old patient diagnosed four years previous with pseudomyxoma peritonei, admitted to the Department of Internal Medicine -Pneumology, with dyspnea, fever, physical asthenia, cramp-like abdominal pain, weight loss. The diagnosis of recurrent pseudomyxoma peritonei has been established following imaging investigations correlated with elevated tumour markers.

Key words: pseudomyxoma peritonei, computed tomography, relapse, ascites

INTRODUCTION

The term of pseudomyxoma peritonei (PMP) was introduced in 1884, used in relation to a mucinous ovarian carcinoma [1]. In 1901, Frankel [2] described another case, one associated with a cyst of the appendix. Overall, the term pseudomyxoma peritonei has been broadly applied to include a heterogeneous assembly of pathological lesions, ranging from benign through borderline to frankly malignant lesions [3].

Pseudomyxoma Peritonei (PMP) represents a recurrent chronic clinical entity, with a low frequency, characterized by accumulation of diffuse intra-abdominal collections of gel (jelly belly) within the peritoneal cavity. This mucin ascites forms from the secretion of the epithelial implants of the epiploon and peritoneum, which in most cases originate from the adenocarcinomas or adenomas of the appendix or the ovary [4].

Pseudomyxoma peritonei constitutes a tumour, of an estimated incidence rate of 1-2 million per year [5].

While the cause of the pathology is the production of mucinous implants and mucin in the abdominal cavity, involving peritoneal surfaces diffusely, PMP as a whole is a poorly understood disease.

In spite of the abdominal viscera being thickly coated with mucus-secreting tumour cells, invasion into extra peritoneal sites or the substance itself does not occur. Instead, the abdominopelvic cavities are slowly filled with semisolid, tenacious, glycoproteins rich neoplastic mucus. This is often organized into large loculated cystic masses [6].

The exact incidence of pseudomyxoma peritonei remains speculative. The clinical caseload experience of the UK national centres (Basingstoke and Manchester), as well as a recent publication from the Netherlands reporting from a nationwide pathological/epidemiological database, suggest a PMP incidence of approximately two per million, per year [7].

CASE REPORT

49-year-old female patient diagnosed three years previously with pseudomyxoma peritonei, admitted to the Department of Internal Medicine-Pulmonology with dyspnea, fever, physical asthenia, cramp-like abdominal pain, weight loss. Symptomatology debuted approximately 10 days previous, heightened in the 24 hours previous to admission.

From the pathological personal history, we note that in July 2013 the patient was diagnosed with appendiceal mucocele and pseudomyxoma peritonei, which prompted surgical intervention, with appendectomy, bilateral ovariectomy and partial omectomy. In 2014, surgical reintervention was performed with total hysterectomy, splenectomy and ablation of hepatogastric ligament with

Received 14th of September 2017. Accepted 10th of October 2017. Address for correspondence: Marius Georgescu, MD, PhD, Assistant Teaching Professor, Department of Functional Sciences, Physiology, Eftimie Murgu Square No. 2A, RO-300041 Timișoara; phone: 0040765527318; e-mail: mgeorgiu83@yahoo.com

total omentectomy, followed by intraoperative intraperitoneal chemotherapy.

On admission, patient appeared to be extremely unwell, presenting the following vital parameters measurements: a body temperature of 38.5 Celsius degrees; a heart rate of 94 beats/minute; oxygen saturation was 93%; respiratory rate was 17 /minute and blood pressure was 110/70 mmHg.

Physical examination revealed abdominal distension accompanied by abdominal tenderness, with no palpable organomegaly or lymphadenopathy. The cardiovascular and respiratory system investigation did not reveal any remarkable changes.The remainder of the physical examination was normal.

Laboratory investigations performed, including full blood count, amylase, liver function tests, urea and electrolytes, were all within normal limits excepting the elevated white blood cells (12 5000/mm^3) ,low hemoglobin level (11.4 g/dl) and high sedimentation rate (79mm). Tumor marker CA19-9 was evaluated and its value was elevated (1240 U/ml).

Thoracic radiography was normal. An abdominal ultrasonography was performed and revealed perigastric fluid collection and echogenic foci in ascites in the pelvic cavity.

Based on clinical examination, laboratory analysis, and abdominal ultrasound, at the time of the investigation the following diagnostic suspicions were raised: peritoneal secondary determinations (peritoneal carcinomatosis) or recurrent pseudomyxoma peritonei.

Computed tomographic scan of abdomen and pelvis demonstrated a large epigastric hypoechoic mass with irregular thickening of the gastric wall and other peritoneal masses with "scalloping effect as well as an iodophil soft-tissue mass 11mm diameter located in the anterior gastric wall (Figures 1, 2 and 3).

Based on the clinical, biological, imagistic chart, the diagnosis of recurrent pseudomyxoma peritonei has been established.

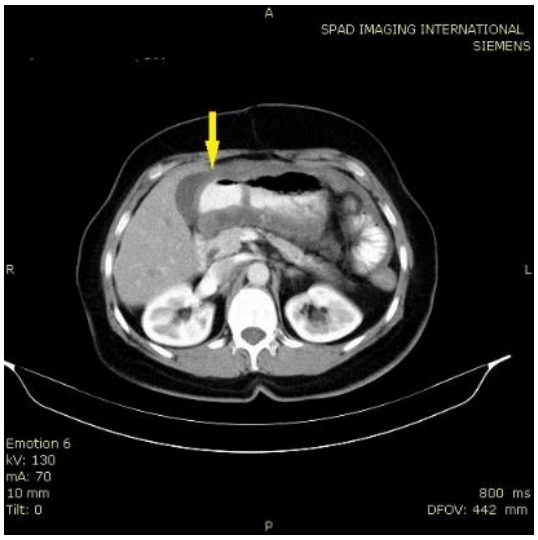

Fig. 1. Abdominal CT scan shows perigastric fluid collection

Fig. 2. CT scan of abdomen and pelvis showing pseudomyxoma peritonei with peritoneal masses (arrow) with "scalloping effect.

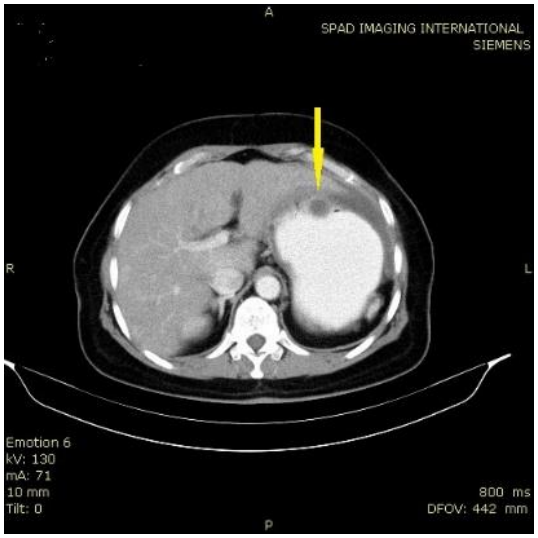

Fig. 3. Iodophil soft-tissue mass located in the anterior gastric wall (arrow)

DISCUSSION

Pseudomyxoma peritonei or jelly belly, is a rare pathological entity with a reserved prognosis, characterized by a complete redistribution of mucin in the peritoneal cavity. Due to the rarity of this disease, the full biological, clinical and pathogenic behaviour is not fully known [8].

Peritoneal jelly disease occurs with a frequency of 2 cases per 10000 laparoscopies (1 case / million / year) and generally affects women with an average age of 53 years, the ratio of women:men being 2-3: 1 [7].

The origin of PMP is considered to be adenomas or mucoscrystalline cystic carcinomas of the appendix and ovary. [9] Other uncommon starting points can be: uterine

carcinomas, colon, collage, pancreas, breast, lung, and testicle. However, the techniques of immunohistochemistry and molecular genetics tests support the hypothesis that for most women the ovarian tumour is secondary to a perforated appendicular mucinous tumour [10, 11].

Symptomology is nonspecific; frequently, the disease is not diagnosed or is confused with other pathologies [12]. The most common symptoms are the progressive increase in abdominal volume, with diffuse abdominal pain. Other possible symptoms are asthenia, weight gain, nausea, vomiting, diarrhoea or urinary symptoms. The patient may present fever, signs of peritoneal irritation with leucocytosis and / or anemia [13].

Our patient was admitted with fever, physical asthenia, cramp-like abdominal pain. She also complained of dyspnoea and weight loss, which are less common symptoms for this pathological entity.

Physical examination in pseudomyxoma peritonei may present a bulky abdomen, organomegaly, bilateral or unilateral ovarian tumours and appendicitis like syndrome [14]. Abdominal distension increases over time, while digestive and cardiorespiratory functional disorders develop. Early stages of the disease are difficult to diagnose, due to the uncharacteristic symptom for PMP.

The pathology is often accidentally discovered during CT investigations and ultrasound for non-specific abdominal symptoms [9, 15].

In our case the patient was already diagnosed with appendicular mucocele and pseudomyxoma peritonei four years previous, followed by surgical intervention, with appendectomy, bilateral ovariectomy and partial omentectomy. A year later a second intervention was necessary with total hysterectomy, splenectomy and ablation of hepatogastric ligament with total omentectomy, followed by intraoperative intraperitoneal chemotherapy.

Patient presented abdominal distension accompanied by abdominal tenderness but no palpable organomegaly or lymphadenopathy was present.

The most frequent investigation for diagnosis is abdominal ultrasonography, in which case commuted tomography – the gold standard – can be used to establish the extent of disease. Moreover, the levels of tumour markers such as CA 19-9 and CEA can be used to establish prognosis [14]. The patient may also present leucocytosis and / or anaemia [13].

Laboratory investigations were assessed and revealed leucocytosis, anemia, high sedimentation rate and elevated tumor marker CA19-9.

CT and ultrasonography have been reported to be helpful in detecting pseudomyxoma peritonei [9, 15]. While computed tomography remains the gold standard for diagnostic imaging, abdominal ultrasonography is low-priced, available in most cases, well tolerated, and can identify most common PMP findings such as ascites and omental caking. Computed tomography shows the following patterns: posterior displacement of the intestines; diffuse peritoneal infiltration appearing similar to ascites; intrahepatic low density attenuated lesions; and (4) scalloping of intra-abdominal organs, especially the liver and the spleen [16].

Both investigations were performed on our patient. Abdominal ultrasonography revealed perigastric fluid collection, echogenic foci in ascites in the pelvic cavity. CT scan of the abdomen and pelvis indicated a large epigastric hypoechoic mass with irregular thickening of the gastric wall and other peritoneal masses with “scalloping effect’’ of the liver as well as an iodophil soft-tissue mass 11mm diameter located in the anterior gastric wall.

A treatment strategy for PMP should pursue complete cytoreduction and prevention of recurrence or progression. Mayo Clinic, Gough DB reported that chemotherapy can improve survival only if administered intraperitoneally [17]. Systemic chemotherapy does not appear to affect prognosis [18].

In the presented case, the patient had been previously diagnosed with appendicular mucocele and pseudomyxoma peritonei. A complete cytoreduction was performed followed by intraoperative intraperitoneal chemotherapy, however after four years pseudomyxoma peritonei relapsed.

In general, surgical reintervention is difficult to perform due to adhesions and fibrosis greatly increasing the risk of unintentional enterotomies, with subsequent formation of fistulae and leaks [19]. Our patient refused a third look surgery.

CONCLUSION

We have described a female patient who developed PMP, a heterogeneous and rare condition as a result of appendiceal tumours and who underwent complete cytoreduction and intraoperative intraperitoneal chemotherapy. After four years relapse of the pseudomyxoma peritonei occurred. Surgery is the election treatment for pseudomyxoma peritonei, although total resection is rarely possible. Because of the low morbidity and slow growth of the tumour, reintervention is indicated for symptoms of recurrence.

REFERENCES

1. Werth R. Pseudomyxoma peritonei. *Arch Gynaecol.* 1884, 24: 100-118.
2. Frankel E. Uher das sogenaute pseudomyxoma peritonei. *Med Wochenschr.* 1901;48:965-970.
3. Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P. Systematic review of the Sugarbaker procedure for pseudomyxoma peritonei. *Br J Surg.* 2005;92(2):153-158.
4. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing

pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei." *Am J Surg Pathol.* 1995;19(12):1390-1408.
5. Bevan KE, Mohamed F, Moran BJ. Pseudomyxoma peritonei. *World J Gastrointest Oncol.* 2010;2(1):44-50.
6. Gupta S, Singh G, Gupta A, et al. Pseudomyxoma peritonei: An uncommon tumor. *Indian J Med Paediatr Oncol.* 2010;31(2):58-61.
7. Loungnarath R, Causeret S, Bossard N, Faheez M, Sayag-Beaujard AC, Brigand C, Gilly F, Glehen O. Cytoreductive surgery with intraperitoneal chemohyperthermia for the treatment of pseudomyxoma peritonei: a prospective study. *Dis Colon Rectum.* 2005;48:1372-1379.
8. Qu Z, Liu L (2006) Management of pseudomyxoma peritonei. World J Gastroenterol 12 (38): 6124-6127.
9. Sugarbaker PH, Ronnett BM, Archer A, Averbach AM, Bland R, Chang D, et al. Pseudomyxoma peritonei syndrome. *Adv Surg.* 1996;30:233–280.
10. Ronnett BM, Zahn CM, Kurman RJ, Kass ME, Sugarbaker PH, Shmookler BM. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". *Am J Surg Pathol.* 1995;19:1390-1408.
11. Smeenk RM, van Velthuysen ML, Verwaal VJ, Zoetmulder FA. Appendiceal neoplasms and pseudomyxoma peritonei: a population based study. *Eur J Surg Oncol.* 2008;34:196-201.
12. Järvinen P, Lepistö A. Clinical presentation of pseudomyxoma peritonei. *Scand J Surg.* 2019;9(4):213-216.
13. Meshikhes AW, Al-Abkari HA, Al-Momen SA, Saad FE. Pseudomyxoma peritonei. *Saudi Med J.* 2006;27(3):389-391.
14. Touloumis Z, Galyfos G, Kavouras N, Menis M, Lavant L. Aggressive Pseudomyxoma Peritonei: A Case Report with an Unusual Clinical Presentation. *Case Reports in Oncological Medicine.* 2013;10:69-73.
15. Bechtold RE, Chen MY, Loggie BW, Jackson SL, Geisinger K. CT appearance of disseminated peritoneal adenomucinosis. *Abdom Imaging.* 2001;26:406-410.
16. Lawate PS, Singh SP, Jasper MP, et al. Computed tomography and sonographic features of pseudomyxoma peritonei. *AJR Am J Roentgenol* 1989;152:429.
17. Gough DB, Donohue JH, Schutt AJ, et al. Pseudomyxoma peritonei. Long-term patient survival with an aggressive regional approach. *Ann Surg.* 1994;219(2):112-119.
18. Kojimahara T, Nakahara K, Shoji T, et al. Identifying prognostic factors in Japanese women with pseudomyxoma peritonei: a retrospective clinico-pathological study of the Tohoku Gynecologic Cancer Unit. *Tohoku J Exp Med.* 2011;223(2):91-96.
19. Al-Buainain H, Al-Jehani Y, Moghazy K, Al-Quorain A. Psuedomyxoma peritonei secondary to adenocarcinoma of the cecum. *J Family Community Med.* 2010;17(2):103-106.

PSEUDOMIXOM PERITONEAL RECIDIVAT. PREZENTARE DE CAZ

REZUMAT

Pseudomixomul peritoneal (PMP) este o entitate patologica rara, cronica, recidivanta cu o incidenţă estimată de 1-2 cazuri la 10000 laparoscopii (1 caz/million/an) caracterizată prin acumularea unor mase semisolide mucinoase relativ transparente în cavitatea peritoneală.

Pseudomixomul peritoneal îmbracă un spectru larg de manifestari, de la benigne la cele ''la limită'' (borderline) şi până la cele maligne.

Prezentam cazul unei paciente in varsta de 49 de ani , diagnosticata in urma cu patru ani cu pseudomixom peritoneal, care se prezinta in Departamentul de Medicina Interna -Pneumologie, acuzand, dispnee, febra astenie fizica, dureri abdominale difuze, scadere ponderala.

In urma investigatiilor imagistice corelate cu valori crescute ale markerilor tumorali s-a stabilit diagnosticul de pseudomixom peritoneal recidivat.

Cuvinte cheie: pseudomixom peritoneal, computer tomograf, recidiva, ascita

DIAGNOSTIC PERFORMANCE OF STRAIN ELASTOGRAPHY FOR THYROID NODULES

MARIA-CRISTINA OPREA[1,2], LAZAR FULGER[3]

[1] Victor Babes University of Medicine and Pharmacy Timisoara, Endocrinology Department
[2] Korall Clinic Satu-Mare
[3] Pius Brinzeu County Clinical Emergency Hospital Timisoara, 2nd Surgery Clinic

ABSTRACT

Thyroid disorders are common and are associated with levels of thyroid-stimulating hormone and iodine availability. Thyroid nodules are among the most prevalent thyroid conditions detected in 50% to 60% of healthy people. Most thyroid nodules are benign, with less than 5% cancerous lesions, and the challenge for clinicians is to accurately discriminate between benign disease and malignancies. US elastography is a recent technique currently used in combination with B-mode ultrasound and is able to provide useful information for the differentiation of benign and malignant nodules based on tissue stiffness/elasticity.

We have analysed 44 thyroid nodules (31 benign, 13 malignant) assessed by means of conventional and Doppler ultrasound, as well as by strain elastography. The ultrasound and strain elastography studies were performed during a single procedure on the same equipment. At conventional ultrasound, except for the presence of halo sign, all the other features (margins, echogenicity, homogeneity, microcalcifications and transonic areas) considered to be predictive of malignancy reached statistical significance. The blood flow assessed by the means of colour-flow Doppler also reached statistical significance.

Strain ratios were recorded for each nodule, with a mean strain ratio value of 1.55 in the benign nodule group and 3.42 in the malignant nodule group and the results obtained at strain elastography were compared with the blinded histological diagnosis. The diagnostic performance of strain elastography proved to be high, with 92.3% sensitivity, 67.7% specificity, 100% positive predictive value and 88.57% negative predictive value, thus being a reliable tool in the differentiation of benign and malignant thyroid nodules.

Keywords: strain elastography, thyroid nodule, thyroid cancer

INTRODUCTION

Thyroid gland is central to metabolic processes, but its structure and function can be affected by various conditions, such as hypo- or hyperthyroidism, goiter, nodules, thyroiditis or cancer. In fact, thyroid disorders are common and are associated with levels of thyroid-stimulating hormone (TSH), being linked with iodine availability, so that goiter is prevalent where iodine is scarce, while autoimmune thyroid conditions are frequent in iodine-replete areas [1]. A recent meta-analysis [2] of studies conducted in Europe between 1975 and 2012 has calculated a mean prevalence of total thyroid dysfunction of 3.82% and an incidence of 259.12/100,000/year, whereas the mean prevalence of undiagnosed thyroid dysfunction was estimated to be as high as 6.71%.

While low TSH levels are seen in people with hyperthyroidism and elevated levels in those with hypothyroidism, goiter and thyroid nodules are present in both settings. Thyroid nodules are among the most prevalent thyroid conditions detected in 50% to 60% of healthy people [3] and their formation is caused by either their fail or their ability to synthesize thyroid hormones regardless of the TSH level. Most thyroid nodules are benign, with less than 5% cancerous lesions, and the challenge for clinicians is to accurately discriminate between benign disease and malignancies. This is important not only for the timely diagnosis of cancer, but also to prevent overtreatment of benign thyroid nodules. During the last two decades, an increased incidence of thyroid cancer has been recorded, so that the estimated worldwide incidence for thyroid cancer in 2012 was 300,000 new cases, out of which more than 1/3 were found in women [4]. This increased incidence is mainly due to the improved detection by new thyroid and neck ultrasound techniques, which made possible the detection of nodules as small as 0.2 cm [5,6].

Received 15th of August 2017. Accepted 10th of October 2017. Address for correspondence: Oprea Maria Cristina, Endocrinology Department, „Victor Babes" University of Medicine and Pharmacy Timisoara, Eftimie Murgu Square No. 2A, RO-300041, Timisoara, Romania; e-mail: mary_mignona@yahoo.com

Diagnosis of thyroid masses includes clinical examination, laboratory tests, fine needle aspiration biopsy (FNAB) and various imaging techniques. Ultrasound (US), measurement of TSH levels and FNAB are the main elements in the management of thyroid nodules [3]. Ultrasound has very good performance in the detection of thyroid nodules, but its ability to discriminate between benign and malignant masses is limited [7,8]. FNAB is therefore recommended for nodules larger than 10 mm and for those with suspicious US features, although its diagnostic value is also limited as up to 30% of results are either non-diagnostic or indeterminate [9,10].

US elastography is a recent technique currently used in combination with B-mode ultrasound and is able to provide useful information for the differentiation of benign and malignant nodules based on tissue stiffness/elasticity [11,12]. Thus, by using a compression force, elastographic techniques enable the assessment of tissue elasticity by measuring the degree of tissue displacement [13], so that hard or firm nodules are associated with a higher risk of malignancy [3].

After reporting on our results using shear-wave elastography [14], we here describe the results obtained on a series of 44 patients with suspicious thyroid nodules who underwent strain elastography.

MATERIALS AND METHODS

Nodules

This retrospective study included 44 nodules found in 31 patients (28 women and 3 men), mean age 52.3 years (min. 17 years, max. 70 years) seen from August 2016 to September 2017 in the Korall Clinic in Satu Mare. All the patients underwent surgery and the final blinded histopathologic diagnosis performed on the excised thyroid tissue served as reference standard. We have included solitary thyroid nodules or multinodular goiter examined by means of elastography, as well as conventional and Doppler ultrasound. The inclusion criterion was the availability of histopathological diagnosis after surgery.

We have recorded the following patient data: gender, age, weight, thyroid volume, nodule localization and sizes, US features, elastographic score and histological diagnosis of the excised nodules.

Equipment and method

Strain elastography was performed by means of an SIUI ultrasound system (Shantou Institute of Ultrasonic Instruments Co., Ltd., China), Apogee 1200 model, using an 8 MHz 50 mm linear transducer. We have first assessed the sonographic features of the nodules by conventional ultrasound, namely nodule number and sizes, aspect of margins, echogenicity, homogeneity, and presence of halo sign, microcalcifications and transonic areas inside nodules. Afterwards, the blood flow was evaluated by means of color-flow Doppler and classified into intranodular, perinodular, intra- and perinodular or absent blood flow. Lastly, we have performed strain elastography, by applying a slight pressure with the hand-held transducer, while the system produced a color-coded image superimposed on the B-mode image, with the images separately displayed on two screens. The region of interest was selected so that to comprise the nodule and a large part of the surrounding thyroid tissue. The qualitative assessment of nodule elasticity provides information on tissue strain and is displayed as a continuum of colors (red-green-blue), with blue for stiff tissue and red for soft tissue. The semiquantitative assessment consists in the characterization by strain ratio, which is calculated as the ratio of strains in the lesion to that of the surrounding parenchyma.

Statistical Analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) programme (version 17.0 for Windows, SPSS Inc., Chicago, Illinois, USA). We split the 44 nodules in two groups, malignant (13 nodules, 29.5%) and benign (31 nodules, 70.5%). All data were compared using a chi square test, with a p-value <0.05 considered to be statistically significant. Histological diagnosis served as reference standard.

RESULTS

Histology

All patients underwent surgical treatment consisting in either lobectomy or total thyroidectomy. After surgery, histopathologic diagnosis was performed by a pathologist who was blinded regarding the elastography findings. A histological diagnosis of malignancy was made in 13 nodules (29.5%), out of which 4 were classical papillary carcinomas, 2 papillary-follicular, 6 microcarcinomas and 1 medullary carcinoma. These malignant nodules were found in 10 patients (7 women and 3 men), six being located in the left lobe and seven in the right lobe. The majority (n=27, 87%) of the 31 benign masses (70.5%) presented as simple or multinodular goiter, 2 were colloid goiters, 1 Hürthle cell adenoma and 1 chronic autoimmune thyroiditis, out of which 18 were found in the right lobe, 12 in the left lobe and one in the isthmus.

Ultrasound

During the conventional US examination, we have recorded nodule length, width and thickness for all masses, the mean values of each revealing no statistically significant differences between malignant and benign nodules. On the contrary, except for the presence of halo sign, all the other features considered to be predictive of malignancy reached statistical significance: margins ($p = 0.000$), echogenicity ($p = 0.002$), homogeneity ($p = 0.057$), microcalcifications ($p = 0.009$) and transonic areas ($p = 0.031$). Then, we have

assessed the blood flow by the means of colour-flow Doppler US and found statistically significant differences between the two groups at a p-value of 0.049.

Strain elastography

The concept of elastography was first demonstrated by Ophir *et al*. [15] in 1991 and became an important diagnostic tool used to assess the elasticity of various tissues in the body, relying on the principle that an externally applied compression leads to tissue deformation, which is smaller in hard tissues. The first type of elastographic technique introduced in clinical practice was strain elastography. Based on the assessment of tissue displacement, strain elastography is able to differentiate benign from malignant masses, providing an objective evaluation of tissue stiffness/elasticity. We have assessed the elasticity of nodules qualitatively, on the color-coded image, and quantitatively, by recording the strain ratios. First method relies on the visual evaluation of the colors displayed on the screen.

We here report on the results of the second method. We have drawn two regions of interest, one comprising the entire nodule and the second including a significant portion of the adjacent thyroid tissue, which was the reference region. Then, the system automatically calculated and displayed the parenchyma-to-nodule strain ratios, *i.e.* the mean strain in the normal thyroid parenchyma divided by the mean strain in the thyroid nodule. With the patient in supine position with the neck extended, the transducer was transversally placed on the thyroid and we assessed each lesion three to five times. The procedure took up to 8 minutes per patient.

The strain ratios ranged from 0.8 to 4 in the entire group of patients. The mean strain ratio value was 1.55 (lowest value 0.8; largest value 2.7) in the benign nodule group and 3.42 in the malignant nodule group (lowest value 1.8; largest value 4). Table I shows the distribution of nodules by the strain ratios, where values greater than 2 were considered to be suggestive of malignancy.

Table I. Strain ratios in the two groups

Benign nodules		Malignant nodules	
Strain ratio	**Patients, n (%)**	**Strain ratio**	**Patients, n (%)**
<1	6 (19.5%)	>2	2 (15.4%)
>1	23 (74.1%)	>3	8 (61.5%)
>2	2 (6.4%)	4	3 (23.1%)

After the histological diagnosis was available, we compared our results with those obtained on histology and concluded that two lesions (one multinodular goiter in the setting of chronic autoimmune thyroiditis and Hürthle cell adenoma) were misclassified, having strain ratios of 2.7 and 3, respectively. The higher strain ratios may be explained in the first case by the presence of autoimmune thyroiditis, known to cause greater tissue stiffness, and by the microcalcifications present in the nodule diagnosed as Hürthle cell adenoma.

However, this did not elicit a significant impact on the study, and the diagnostic performance of strain elastography proved to be high, with 92.3% sensitivity, 67.7% specificity, 100% positive predictive value and 88.57% negative predictive value. We found a strain ratio 2 to be the best cut-off value (area under the curve of 0.968), as obtained with receiver operating characteristic (ROC) curve analysis (Fig. 1).

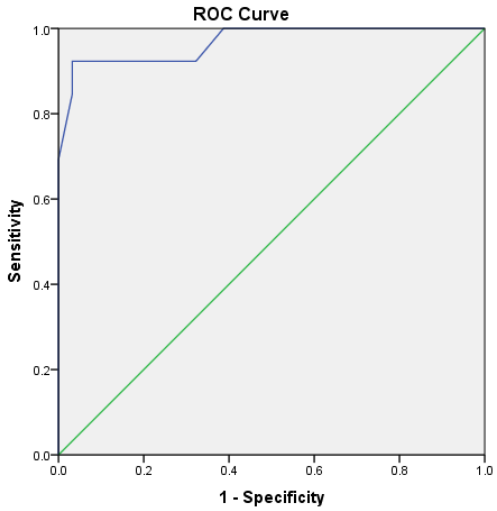

Fig. 1. ROC curve for strain elastography

DISCUSSIONS AND CONCLUSION

Strain elastography relies on the measurement of tissue elasticity and provides valuable information, in addition to those obtained by conventional ultrasound. Current guidelines [3,8,16] state US features considered suggestive of malignancy are not enough sensitive, nor specific to allow detection of all malignant nodules. Instead, elastography has been proved to be a promising diagnostic tool, although further studies are needed to validate it.

Various studies on the use of strain elastography in differentiating benign from malignant thyroid nodules reported this method may predict malignancy with very good specificity and sensitivity. Among the pioneering studies, Lyshchik *et al*.[17] showed that off-line processed elastograms with a strain index above 4 was the strongest predictor of malignancy, exhibiting 96% specificity and 82% sensitivity. At the time, however, the criteria (margin regularity and tumor area ratio) used for real-time elastographic images, although showing high specificities, had low sensitivities. Only two years after, Rago *et al*.[12] used the elasticity score for thyroid nodule elastography and concluded that scores 4 to 5 were highly predictive of malignancy, with 97% sensitivity, 100% specificity and positive predictive value, an 98% negative predictive value.

The semiquantitative approach was also proved to be accurate in diagnosing malignant thyroid nodules, as shown by the study of Cantisani *et al*.[18] who reported 93% sensitivity, 89% specificity, 82% PPV and 94% NPV. The authors concluded that a strain ratio greater than 2 should prompt further investigation. Another study [19] that intended to assess the clinical value of strain ratio, as compared with the elasticity score, found 81% sensitivity and 83% specificity for the former. Similar to these studies, our retrospective analysis shows that a strain ratio score above 2 is highly predictive of malignancy, with 92.3% sensitivity, 67.7% specificity, 100% positive predictive value and 88.57% negative predictive value. In our study, the results obtained at elastography also correlated with findings on conventional and color-flow Doppler ultrasound.

In spite of the two false positive results we found, which may be explained by the presence of thyroid pathologies that cause greater tissue stiffness, in this study all malignancies were correctly diagnosed. In conclusion, strain elastography is a reliable tool for diagnosing malignant thyroid nodules, given that an accurate diagnosis is critical for timely, effective therapy.

REFERENCES

1. Vanderpump MPJ. The epidemiology of thyroid disease. *British Medical Bulletin*. 2011;99:39-51.
2. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *The Journal of Clinical Endocrinology & Metabolism.* 2014;99(3):923-31.
3. Gharib H, Papini E, Garber JR, Duick DS, Harrell RM, Hegedüs L, Paschke R, Valcavi R, Vitti P. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for The Diagnosis and Management of Thyroid Nodules-2016 Update. *Endocrine Practice.* 2016;22(Suppl 1).
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer.* 2015;136(5):E359-86.
5. Brito JP, Morris JC, Montori VM. Thyroid cancer: zealous imaging has increased detection and treatment of low risk tumours. *BMJ* 2013;347:f4706.
6. Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, Negri E. Thyroid cancer mortality and incidence: a global overview. *International Journal of Cancer*. 2015;136(9):2187-95.
7. Moon HG, Jung EJ, Park ST, Ha WS, Choi SK, Hong SC, Lee YJ, Joo YT, Jeong CY, Choi DS, Ryoo JW. Role of ultrasonography in predicting malignancy in patients with thyroid nodules. *World Journal of Surgery*. 2007;31(7):1410–1416.
8. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer: the American Thyroid Association (ATA) guidelines taskforce on thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19(11):1167-214.
9. Redman R, Zalaznick H, Mazzaferri EL, Massoll NA. The impact of assessing specimen adequacy and number of needle passes for fine-needle aspiration biopsy of thyroid nodules. *Thyroid.* 2006;16:55–60.
10. Tee YY, Lowe AJ, Brand CA, Judson RT. Fine-needle aspirationmaymiss a third of allmalignancy in palpable thyroid nodules: a comprehensive literature review. Annals of Surgery. 2007;246(5):714–720.
11. Gharib H, Papini E. Thyroid nodules: clinical importance, assessment, and treatment. *Endocrinology and metabolism clinics of North America*. 2007 Sep 30;36(3):707-35.
12. Rago T, Santini F, Scutari M, Pinchera A, Vitti P. Elastography: new developments in ultrasound for predicting malignancy in thyroid nodules. *J Clin Endocrinol Metab.* 2007;92(8):2917-22.
13. Kwak JY, Kim EK. Ultrasound elastography for thyroid nodules: recent advances. Ultrasonography. 2014;33(2):75-82.
14. Oprea MC, Fulger L. Usefulness of real-time shear wave elastography in the diagnosis of malignant thyroid nodules in patients with autoimmune thyroiditis. *Fiziologia-Physiology.* 2016;26(4).
15. Ophir J, C´espedes I, Ponnekanti H, Yazdi Y, Li X. Elastography: a quantitative method for imaging the elasticity of biological tissues. *Ultrasonic Imaging.* 1991;13(2):111–134.
16. Cosgrove D, Barr R, Bojunga J, Cantisani V, Chammas MC, Dighe M, Vinayak S, Xu JM, Dietrich CF. WFUMB Guidelines and Recommendations on the Clinical Use of Ultrasound Elastography: Part 4. Thyroid. Ultrasound in Medicine & Biology. *Ultrasound Med Biol.* 2017;43(1):4-26.
17. Lyshchik A, Higashi T, Asato R, Tanaka S, Ito J, Mai J, Pellot-Barakat C, Insana MF, Brill AB, Saga T, Hiraoka M, TogashiK. Thyroid gland tumor diagnosis at US elastography. *Radiology* 2005;237:202-211.
18. Cantisani V, D'Andrea V, Biancari F, Medvedyeva O, Di Segni M, Olive M, Patrizi G, Redler A, Enrico De Antoni E, Masciangelo R, Frezzotti F. Prospective evaluation of multiparametric ultrasound and quantitative elastosonography in the differential diagnosis of benign and malignant thyroid nodules: preliminary experience. *European Journal of Radiology*. 2012;81(10):2678-83.
19. Ning CP, Jiang SQ, Zhang T, Sun LT, Liu YJ, Tian JW. The value of strain ratio in differential diagnosis of thyroid solid nodules. *European Journal of Radiology*. 2012;81(2):286-91.

PERFORMANȚA DIAGNOSTICĂ A ELASTOGRAFIEI STRAIN PENTRU NODULII TIROIDIENI

REZUMAT

Tulburările glandei tiroide sunt frecvente și se asociază cu nivelurile hormonului de stimulare tiroidiană și cu disponibilitatea iodului. Nodulii tiroidieni se numără printre bolile tiroidiene cu cea mai mare prevalență, fiind detectați la 50% - 60% dintre persoanele sănătoase. Majoritatea nodulilor tiroidieni sunt benigni, mai puțin de 5% fiind maligni, iar disciminarea cu precizie între boala benignă și cancer reprezintă o provocare pentru clinicieni. Elastografia este o tehnică recentă, utilizată în prezent împreună cu ecografia în mod B, oferind informații utile pentru diferențierea între nodulii benigni și cei maligni pe baza durității / elasticității țesutului.

Am analizat 44 de noduli tiroidieni (31 benigni, 13 maligni) prin ecografie convențională și Doppler, precum și prin elastografie. Studiile ecografice și elastografice de tip *strain* au fost realizate în cursul unei singure proceduri, utilizând același echipament. La ecografia convențională, cu excepția prezenței haloului, toate celelalte caracteristici (contur, ecogenitate, omogenitate, microcalcificări și zone transonice) considerate sugestive pentru malignitate au avut semnificație statistică. Fluxul sangvin, evaluat prin examen Doppler vascular, s-a dovedit, de asemenea, semnificativ din punct de vedere statistic.

Scorurile cantitative (*strain ratios*) au fost înregistrate pentru fiecare nodul, cu o valoare medie de 1.55 în grupul nodulilor benigni și 3.42 în cel al nodulilor maligni, iar rezultatele obținute la elastografia *strain* au fost comparate cu diagnosticul histopatologic realizat de un anatomo-patolog care nu cunoștea rezultatele investigațiilor imagistice. Performanța diagnostică a elastografiei *strain* s-a dovedit a fi foarte bună, cu sensibilitatea de 92.3%, specificitatea 67.7%, valoarea predicitvă pozitivă 100% și valoarea predictivă negativă 88.57%, fiind, așadar, un instrument valoros în diferențierea nodulilor tiroidieni benigni de cei maligni.

Cuvinte cheie: elastografie strain, nodul tiroidian, cancer tiroidian

THE GLOBAL SOCIAL FUNCTIONING OF PATIENTS WITH BIPOLAR AFFECTIVE DISORDER WITH FIRST-RANK SYMPTOMS

RIVIȘ IOANA-ALEXANDRA[1], BARBOIANU RUXANDRA[1], HOMOROGAN CLAUDIA[1], ROMOȘAN ANA-MARIA[1], PAPAVĂ ION[2], HOGEA LAVINIA MARIA[3], BREDICEAN ANA CRISTINA[2]

[1]Timișoara County Emergency Clinical Hospital "Pius Brînzeu", Psychiatry Clinic "Eduard Pamfil"
[2]Victor Babeș University of Medicine and Pharmacy Timișoara, Timișoara County Emergency Clinical Hospital "Pius Brînzeu", Psychiatry Clinic "Eduard Pamfil"
[3]Victor Babeș University of Medicine and Pharmacy Timișoara, Discipline of Psychology, Department of Neurosciences

ABSTRACT

Introduction. One important factor that must be taken into consideration when talking about a patient's quality of life, is the degree of social functioning. Our patients` social functioning represents a topic of maximum interest for the psychiatry specialists, the patients and for their family.

Objectives. This study serves the purpose of evaluating the global social functioning, the marital status, as well as the professional life of patients diagnosed with Bipolar Affective Disorder (BAD).

Material and methods. We have analyzed a group of 34 patients diagnosed with BAD, who had a continuity in diagnosis of over 9 years.

We have applied the Global Assessment of Functioning Scale (GAFS) to patients in remission during their last visit in the outpatient ambulatory system.

Results. We have obtained significant differences between the marital status at the debut of the disorder and the one reported during the last hospital admission (p=0.19).

Also, there were significant differences between the professional status reported during the first episodes of BAD and the one reported during the last hospital admission (p=0.000).

The GAFS reported statistical significant differences between the two sexes (p=0.033).

There were no evidences to support the fact that the presence of FRS (first-rank symptoms) might directly influence a patients social functioning, marital status or professional status.

INTRODUCTION

Differentiation between the psychosis from bipolar affective disorder, schizophrenia and schizoaffective disorder has always been somewhat of a challenge for any psychiatry clinician. Kurt Schneider was concerned with elaborating a series of criteria in order to improve the methods of diagnosis in psychiatry. He discovered that a number of symptoms are most often found in schizophrenia; we know them today as Schneiderian first-rank symptoms (FRS).

Even though experience has taught us that FRS are not pathognomonic for schizophrenia and can appear in any psychotic episode, this topic represents a permanent issue of maximum interest amongst psychiatry specialists.

The purpose of this study is to determine if the presence of FRS at a patient with Bipolar Affective Disorder affects the long-term prognosis and the quality of life from a professional, social and personal point of view. We have tried to limit ourselves to a specific First-Rank Symptom (transparence-influence) and see how the presence of this symptom has affected the life and evolution of a patient.

MATERIAL AND METHOD

A number of 34 patients with bipolar affective disorder were admitted in this study. The cases presented in this study have had a continuity in diagnosis of over 9 years and a long-term evolution, also over 9 years.

Received 12th of August 2017. Accepted 15th of September 2017. Address for correspondence: Claudia Homorogan, MD, Emergency Clinical Hospital "Pius Brînzeu" Timisoara, Liviu Rebreanu Bd. 156, Timisoara, RO-300723, Psychiatry Clinic "Eduard Pamfil" Timișoara; phone: 0746-160322; e-mail: claudiah_15@yahoo.com

All the patients in this study have had psychotic episodes at least once throughout the evolution of the disorder. 20 patients have had FRS at least once during the evolution of the disorder, without having the diagnosis changed and the other 20, have never had FRS. The data was collected from the cases Registry in The Psychiatric Clinic of Timisoara, from the patients' medical records, from interviews that took place between years 1978 and 2016.

Criteria for inclusion:

1. Patients diagnosed with Bipolar Affective Disorder, according to the ICD-10 criteria, with an evolution of at least 9 years with this diagnosis.
2. Patients that have been and still are under medical supervision through the psychiatric ambulatory system in Timisoara from onset until present time.
3. Patients that have had at least one psychotic episode since first diagnosed until present.

Criteria for exclusion:

1. History of substance abuse.
2. The presence of another psychiatric pathology.

We collected socio-demographical data, age of onset, family history of psychiatric disorders, number of admittances in the hospital, level of education, marital status and applied the GAFS during the last visit in the ambulatory system.

The cases have been divided into two groups:

a) Group A included 17 patients who presented FRS during at least one psychotic episode.
b) Group B involved a number of 17 patients who have never presented FRS.

The data has been processed in SPSS, using non-parametric tests, seeing as the data does not respect the normal distribution condition required for parametric tests.

RESULTS

The group included into the study is composed of 9 men and 25 female patients that have had a period of evolution of the Bipolar Affective Disorder of 9 or more years.

Out of the total of 34 patients, an equal percentage of patients (23.53%) have had the age of onset between 15-20 years and over 35 years. A percentage of 17.65 have had a debut of the disorder between 20-25 years, 26.47% of them, between 25 and 30 years. A small percentage (8.82%) have had the debut of the disorder between 30 and 35 years old (Figure 1).

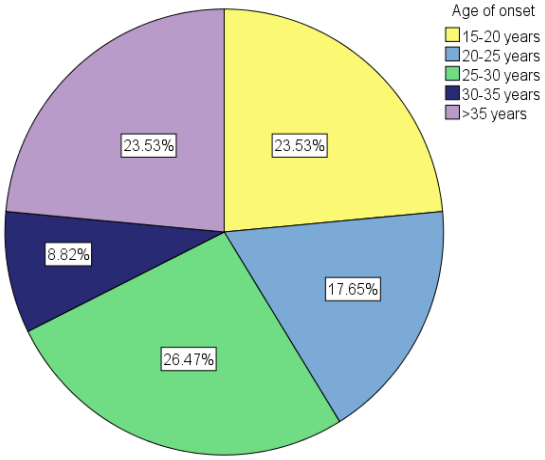

Fig. 1. Age of onset of the disorder (entire group)

The average age of onset of the disease, amongst out patients is 28.56, as shown below (Table I).

Table I. Age of onset

Age of onset

Mean	N	Std. Deviation
28.56	34	9.365

The further analysis of the age of onset in group A (patients who have presented TI throughout the evolution of the disorder) has revealed that a percentage of 11.76% have had the debut of the disorder between 30-35 years old and over 35 years.

Equal percentages (29.41%) have had the debut of the disorder between 15 and 20 years old and 25-30 years of age. 17,65% have had the first episode during 20 and 25 years old (Figure 2).

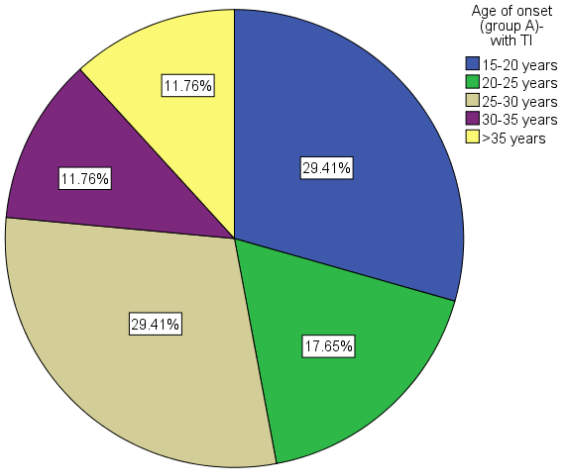

Fig. 2. Age of onset of the disorder in group A (patients who presented TI).

As for group B (patients who have never presented TI), an equal percentage of 17.65 have had their first symptoms appear between the ages of 15-20 years and between 20-25 years of age. 23.53% have had their debut of the disorder between the ages of 25-30 years old, 5.88% between 30-35 years old and 35.29% over the age of 35 (Figure 3).

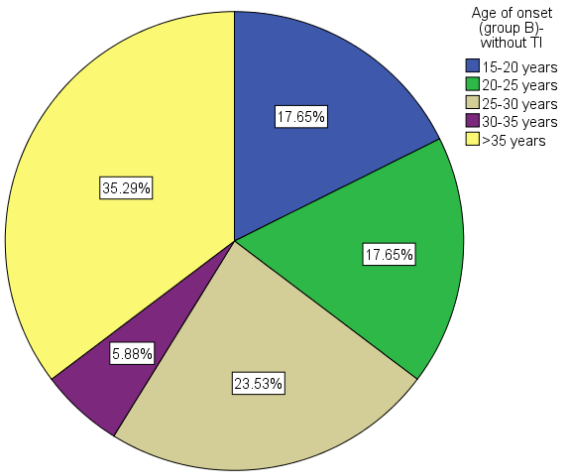

Fig. 3. Age of onset of the disorder in group B (patients who have never presented TI)

We have also established the types of episodes presented most often by the 34 patients included in our study. Equal percentages, of 17.65% have has most often depressive episodes and manic episodes with psychotic symptoms. A majority of 38.24% have had mostly manic episodes without psychotic symptoms and 26.47%, mixed episodes.

In group A, a majority of 35.29% have had mostly manic episodes with psychotic symptoms, equal percentages of 23.53 have presented most often depressive episodes and manic episodes and 17.65% mixed episodes.

As for the patients included in group B, a majority of 52.94% have had most often manic episodes without psychotic symptoms, 35.29% have had mostly mixed episodes and a percentage of 17.76 have had mostly depressive episodes without psychotic symptoms.

There have been no significant differences between the two groups regarding the number of episodes which needed hospital admission.

We compared the GAFS scores between the two sexes, obtaining significant differences (p=0.033, 2-tailed). The same GAFS scores showed no significant differences when comparing the two groups, A and B.

As for the marital status reported at the debut of the disorder, compared to the one declared during the last hospital admission, we have detected a statistical significance (p=0.011). If at the debut of the disorder 55.88% of the patients were married, when last evaluated, after 9 or more years of BAD, only 44.12% remain married. Also at the debut, a percentage of 8.82 were divorced, whereas now, 32.35% of the patients are divorced or separated.

While discussing the professional status, the one declared by the patient at his first episode of BAD, compared to the professional status established during the last admission, there were highly significant differences (p=0.000).

DISCUSSION

The presence or absence of FRS in patients with BAD, evidently has a serious impact on both the patient and on the immediate family members, even though it may not directly influence the patients` personal, professional life and his overall ability to function well in a society.

What we have established with certainty is that patients with BAD suffer from a severe alteration of their social, professional and personal life because of this specific disorder. Taking into consideration that this is a chronic disorder, focusing on these particular aspects starting from the first episode, might have a significant long-term impact.

This study is not without limitations, taking into consideration that we have been able to select only a small number of patients, for which we have had accurate and precise information.

REFRENCES

1. DeVylder JE, Burnette D, Yang LH. Co-occurrence of psychotic experiences and common mental health conditions across four racially and ethnically diverse population samples. *Psychol Med.* 2014; 44:3503-3513.
2. Dunayevich E, Keck PE. Prevalence and description of psychotic features in bipolar mania. *Curr Psychiatry Rep.* 2000; 2:286-290.
3. World Health Organization. 1992. The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines. Geneva: World Health Organization.
4. Allardyce J, McCreadie RG, Morrison G, van Os J. Do symptom dimensions or categorical diagnoses best discriminate between known risk factors for psychosis? *Soc Psychiatry Psychiatr Epidemiol.* 2007; 42(6):429-37.
5. Kitamura T, Okazaki Y, Fujinawa A, Yoshino M, Kasahara Y. Symptoms of psychoses. A factor-analytic study. *Br J Psychiatry.* 1995; 166(2):236-40.
6. Goes FS, Zandi PP, Miao K, et al. Mood-incongruent psychotic features in bipolar disorder: familial aggregation and suggestive linkage to 2p11-q14 and 13q21-33. *Am J Psychiatry.* 2007; 164(2):236-47.
7. Van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med.* 2009; 39(2): 179-95.
8. Kim MD, Seo HJ, Yun HJ, Jung YE, Park JH, Lee CI, et al. The Relationship between Cognitive Decline and Psychopathology

in Patients with Schizophrenia and Bipolar Disorder. *Clin Psychopharmacol Neurosci.* 2015; 13(1):103-8.

9. American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5(5th ed.). Arlington, VA: American Psychiatric Association.

FUNCȚIONAREA SOCIALĂ GLOBALĂ A PACIENȚILOR CU TULBURARE AFECTIVĂ BIPOLARĂ CU SIMPTOME DE PRIM RANG

REZUMAT

Introducere. Un factor important care trebuie luat în considerare când vorbim despre calitatea vieții pacienților este gradul de funcționare socială. Funcționarea socială a pacientului reprezintă un subiect de interes maxim pentru medicii psihiatri, pentru pacienți și pentru familiile acestora.

Obiective. Acest studiu este destinat evaluării funcționării sociale globale, statusului marital, precum și al vieții profesionale a pacienților diagnosticați cu tulburare afectivă bipolară (Bipolar Affective Disorder - BAD).

Materiale și metode. Am analizat un grup de 34 de pacienți diagnosticați cu BAD, care au avut o continuitate în diagnosticare de mai mult de 9 ani. Am aplicat testul de evaluare globală a scării funcționale (Global Assessment of Functioning Scale - GAFS) la pacienții aflați în remisiune, în timpul ultimei vizite în ambulatorul de specialitate.

Rezultate. Am obținut diferențe semnificative în ceea ce privește statusul marital al pacienților la debutul afecțiunii și cel raportat la ultima internare spitalicească (p=0.19). De asemenea, au existat diferențe semnificative între statusul profesional la debutul primelor episoade de BAD și cel raportat la ultima internare în spital (p=0.000). Testul GAFS a relevat diferențe semnificative între cele două sexe (p=0.033).

Nu au existat dovezi referitoare la faptul că simptomele de prim rang (first-rank symptoms - FRS) ar putea influența direct funcționarea socială a pacientului, statusul marital sau profesional.

SYSTOLIC LEFT VENTRICULAR FUNCTION EVALUATED WITH TWO DIMENSIONAL AND THREE DIMENSIONAL SPECKLE TRACKING ECHOCARDIOGRAPHY IN ELITE RUGBY PLAYERS

IRINA POPESCU[1,2], SILVIA MANCAS[1,2], IOAN SERBESCU[3], CRISTIAN MORNOS[1,2], ADINA IONAC[1,2]

[1] Institute of Cardiovascular Diseases Timisoara, Romania
[2] "Victor Babes" University of Medicine and Pharmacy Timisoara, Romania
[3] County Hospital, Sportive Medicine Ambulatory, Timisoara, Romania

ABSTRACT

Background: The athlete's heart is associated with physiological adaptation remodeling due to effort training protocols. These effects on left ventricular (LV) strain were equivocal and the results in literature are controversial. The aim of our study was to evaluate LV systolic deformation in elite rugby players using two new echocardiographic methods: two-dimensional (2D) speckle tracking method and three-dimensional speckle tracking echocardiography (3D STE).

Methods: 26 male rugby players underwent standard 2D and 3D echocardiography at rest. LV global systolic longitudinal strain (GLS) was assessed by speckle tracking methods using both 2D and 3D echocardiography.

Results: We found statistically significant positive correlations between 2D GLS and interventricular septum thickness (IVST), posterior wall thickness (PWT), 3D GLS ($p<0.05$, $r<0.75$) and negative correlation with mitral and tricuspid annular systolic excursion (MAPSE) ($p=0.034$), respectively TAPSE ($p=0.041$). Also a negative correlation was detected with 3D ejection fraction (EF) ($p=0.016$).

We also found a significant positive correlation between 3D GLS and body mass index (BMI) ($p=0.032$), A'lat velocity of mitral annulus ($p=0.049$), 2D GLS ($p=0.006$) and a negative correlation with E velocity of mitral inflow ($p=0.03$), E' lat and E ' med velocity of mitral annulus ($p=0.002$, respectively $p<0.001$), 3D EF ($p=0.04$), the strongest correlation being with E' med ($p<0,001$, $r= -0.816$). By linear regression analyses, 3D GLS was independently associated with E' med, E' lat and 2D GLS, adjusted value of R square coefficient showing that 76% of the 3D GLS variability can be predicted by the variation of the independent variables included in the model.

Conclusions: 2D and 3D STE are new and feasible technique for assessing LV myocardial deformation in athletes. We concluded that athletes with the highest LV physiological hypertrophy had the most increased longitudinal systolic function, in opposite with hypertensive patients with pathological LV hypertrophy, where 2D GLS was found significantly decreased.

Keywords: athlete, speckle tracking, strain, systolic left ventricular function.

INTRODUCTION

New echocardiographic techniques such as Speckle tracking and three-dimensional (3D) echocardiography have already demonstrated an important role in evaluation of left ventricular (LV) systolic and diastolic function in elite athletes [1-4]. Physiological LV hypertrophy in athlete's heart is a complex adaptive mechanism, a response of the heart to intense effort training programs. It is well known that endurance training protocols in athletes (aerobe sports) increases LV volumes (eccentric hypertrophy) and strength efforts (anaerobe sports) predominantly increases LV wall thickness (concentric hypertrophy). In real life, there is no sport in which the type of effort is only aerobe or anaerobe and that's the reason why athletics' heart has usually mix hypertrophy (volume load plus pressure load adaptation) [5-6].

The aim of our study was to evaluate LV systolic deformation in an elite rugby players' team using two dimensional (2D) speckle tracking method and 3D speckle tracking echocardiography (STE). The reason for choosing this hypothesis is the fact that this issue represent controversial even in the last research. Two-dimensional global longitudinal strain (2D GLS) of athletes appeared to

Received 10th of October 2017. Accepted 15th of November 2017. Address for correspondence: Irina Popescu, MD, PhD, Institute of Cardiovascular Diseases Timisoara, Gheorghe Adam 13 A, Timisoara, Romania; phone: 0040744687019; e-mail: irinap75@yahoo.com

be significantly increased at rest in comparison with healthy subjects [4,7-8]. Other studies showed no change in 2D GLS in athletes [9]. and in few other observations, 2D GLS was lower than in controls [10-11].

By using 3D speckle tracking method, 3D GLS in athletes did no differ from sedentary controls in one study [12] and in other, 3D GLS was even lower than in sedentary normals [13].

The difference between 3D and 2D STE strain analysis consists mainly in the advantage to asses LV deformation inside a volumetric single image rather than bidimensional multiple images, to calculate all the strain data at the same heart rate in a single heart beat acquisition.

So, given the latest data in this area, the aim of our study was to analyze myocardial strain parameters (GLS) using both STE methods (2D and 3D GLS evaluation) in a team of elite rugby players.

MATERIAL AND METHODS

Twenty six male athletes from the regional rugby players' team (part of Romanian national rugby team) were evaluated in the Institute of Cardiovascular Diseases Timisoara, Romania. All of the subjects were engaged in a training programme of at least 25 ours/week in the last year. All participants gave written informed consent to the procedures included in our study. The athletes underwent a complete 2D and 3D transthoracic echocardiographic exam at rest. Within the clinical examination were measured: weight (W), height (H), body surface area (BSA) (after diagram Du Bois) [14], body mass index (BMI).

Standard transthoracic bidimensional (2D) echocardiographic study was performed by an experienced echocardiographer using a Vivid E9 ultrasound machine (GE Healthcare) with an M5S probe. All athletes were examined in the left lateral position.

Standard 2D measurements - LV diastolic diameter (LVDD) and LV systolic diameter (LVSD), interventricular septum thickness (IVST) and posterior wall thickness (PWT) - were obtained in the parasternal long axis view [15]. LV mass was automated calculated according to the ASE recommendations [16]. LV end diastolic and endsystolic volumes (LVEDV, LVESV) were obtained in the apical four and two chamber view. LV ejection fraction (EF) was calculated using the Simpson biplane method [16-17]. Resting LV diastolic function was assessed by E and A wave velocities from the mitral inflow. Left atrium (LA) volume was assessed in ventricular end-systole by the modified Simpson's monoplane method in the apical four-chamber and two-chamber view according to the guidelines [18].

Pulsed tissue Doppler imaging data were obtained from a 2 mm sample volume placed at the lateral mitral annulus and medial mitral annulus in the apical 4 chamber view recorded during an end-expiratory apnea period [19].

Mitral respective tricuspid annular plane systolic excursion (MAPSE respective TAPSE) was calculated by the difference between end-diastolic and end-systolic measurements (mm) [19-20].

For 2D Speckle tracking evaluation, global longitudinal strain (2D GLS) was computed from high frame rate (>50 frame/sec) apical views (four chambers, two chambers and three chambers) using speckle tracking analysis (Echo Pac, Version 12BT, GE Healthcare). 2D GLS was obtained by averaging the segmental strain curves of all 17 segments of LV [21-23] and was represented in a color coded bull's eye plot (Figure 1).

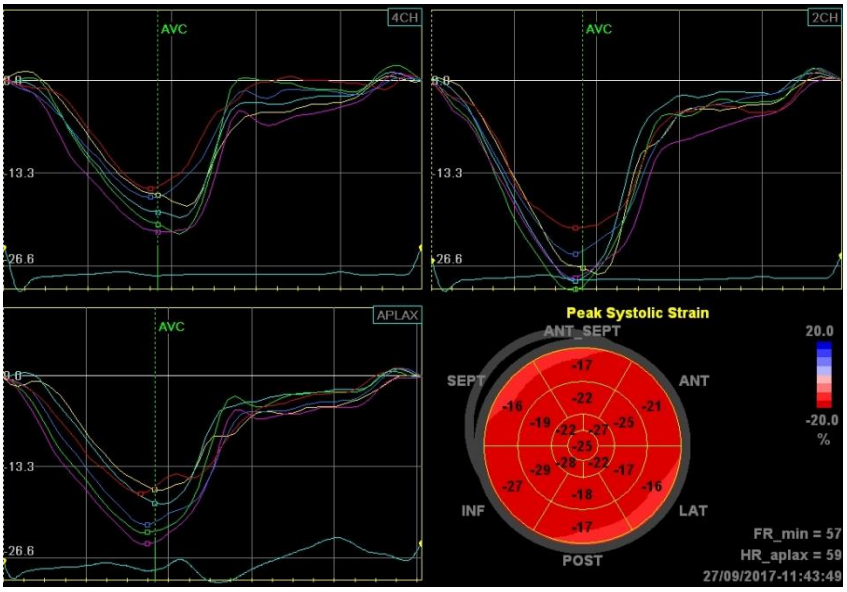

Fig. 1. Speckle tracking imaging with normal representation of 2D GLS (strain curves and bull's eye plot)

Real time three dimensional (3D) echocardiography data set acquisitions were acquired by the same examiner using a 3V matrix array transducer (GE Healthcare). A full volume data set of the LV was acquired from apical view, consisted in four consecutive beats ECG-gated subvolumes at the end of expiration and breathe holding. Two or three datasets for patient were obtained, stored and exported to an off-line workstation for further analysis (Echo Pac, Version 12BT, GE Healthcare). With a specific software algorithm (4D AutoLVQ™ – GE Healthcare), LV volumes, LV EF, LV Mass and 3D global longitudinal strain (3D GLS) were calculated according to actual recommendations [21-23]. All steps were followed as described in the previous studies [24-25]:

- Automatic slicing of the entire full LV volume dataset
- Automatic alignment of all the three planes from apical view
- Identification of LV endocardial border both in diastole and systole (automatic with manual correction if necessary) with calculation of LVEDV and LVESV
- Analysis and data display (EF % = LVEDV-LVESV/LVEDV x100)
- Further evaluation of LV mass and strain were calculated using automatic border detection of epicardium (with optional manual correction).

LV Mass = (LV epicardial volume –LV endocardial volume) x1.05.

3D LV mass was indexed for height powered to 2.7.

3D GLS was automated generated and presented in regional and average strain curves and also in color-coded 17 segments bull's eye plot

Statistical analysis of the data was performed with SPSS 17 software. Clinical and echocardiographic characteristics are presented as mean value ± standard deviation (SD) using descriptive analysis. Pearson's correlation was used to evaluate statistical significant correlations of a given Gaussian variable, while linear regression analysis was used to assess the variation of 3D GLS, a dependent variable by using different predictor variables as independent variables. The null hypothesis was rejected at $p \leq 0.05$.

RESULTS

Physical and echocardiographic characteristics of the entire group of athletes were illustrated in Table I.

Table I. Physical and echocardiographic characteristics data of entire group of athletes

Characteristics	Mean±standard deviation	Characteristics	Mean±standard deviation
Age (years)	25.77±3.32	E (m/s)	0.85±0.15
Height (H) (cm)	182.88±7.02	A (m/s)	0.42±0.09
Weight (W) (kg)	101.77±15.15	S' lat (m/s)	0.10±0,01
BMI (kg/m^2)	30.37±3.75	E' lat (m/s)	0.17±0.04
BSA (m^2)	2.23±0.18	A' lat (m/s)	0.07±0.02
LVEDD (cm)	5.28±0.43	S' med (m/s)	0.14±0.20
LVESD (cm)	3.47±0.36	E' med (m/s)	0.12±0.02
IVST (cm)	1.19±0,11	A' med (m/s)	0.07±0.01
PWT (cm)	1.17±0,12	MAPSE (mm)	20.04±1.90
LVEDV (ml)	145.38±37.86	TAPSE (mm)	29.88±4.81
LVESV (ml)	59.34±15.75	2D GLS (%)	-18.01±2.12
LVEDVi (ml)	67.11±9.16	3D GLS (%)	-15.99±2.70
LVESVi (ml)	27.63±3,88	3D LVEDV (ml)	166.12±25.37
2D EF (%)	.58±0.04	3D LVESV (ml)	71.27±13,95
LVMi (mg)	136.89±16,73	3D EF(%)	0.56±0.03
LAA (cm^2)	22.17±3.55	3D LVM(mg)	139.92±12.81
LAV (ml)	69.12±17.73		

Legend: BMI, body mass index; BSA body surface area; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVST, interventricular septum thickness; PWT, posterior wall thickness; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEDVi, LVEDV index, LVESVi, LVESV index; 2D EF, two-dimensional ejection fraction; LVMi, left ventricular mass index; LAA, left atrial area; LAV, left atrial volume; E, peak E velocity; A, peak A velocity; S' lat, peak S' velocity of lateral mitral annulus; E' lat, peak E' velocity of lateral mitral annulus; A' lat, peak A' velocity of lateral mitral annulus; S' med, peak S' velocity of medial mitral annulus; E' med, peak E' velocity of medial mitral annulus; A' med, peak A' velocity of medial mitral annulus; MAPSE, mitral annulus plane systolic excursion; TAPSE, tricuspid annulus plane systolic excursion; 2D GLS, two-dimensional global longitudinal strain; 3D GLS, three-dimensional global longitudinal strain; 3D LVEDV, three-dimensional LVEDV; 3D LVESV, three-dimensional LVESV; 3D EF, three-dimensional ejection fraction; 3D LVM, three-dimensional left ventricular mass.

We found statistically significant positive correlations between 2D GLS and IVST, PWT, 3D GLS ($p<0.05$, $r<0.75$) and negative correlation with MAPSE ($p=0.034$), TAPSE ($p=0.041$) and 3D EF ($p=0.016$) (Table II).

Table II. Significant correlation of 2D GLS

2D GLS	Correlated variables	Pearson correlation coefficient (r)	p
	IVST	0.423	0.035
	PWT	0.590	0.002
	MAPSE	-0.425	0.034
	TAPSE	-0.412	0.041
	3D GLS	0.571	0.006
	3D EF	-0.478	0.016

Legend: 2D GLS, two-dimensional global longitudinal strain; IVST, interventricular septum thickness; PWT, posterior wall thickness; MAPSE, mitral annulus plane systolic excursion; TAPSE, tricuspid annulus plane systolic excursion, 3D GLS, three-dimensional global longitudinal strain; 3D EF, three-dimensional ejection fraction.

We also found a significant positive correlation between 3D GLS and BMI ($p=0.032$), A'lat ($p=0.049$), 2D GLS ($p=0.006$) and a negative correlation with E ($p=0.03$), E' lat ($p=0.002$), E' med ($p<0.001$), 3D EF ($p=0.04$), the strongest correlation being with E' med ($p<0,001$, $r= -0.816$) (Table III).

Table III. Significant correlations of 3D GLS

3D GLS	Correlated variables	Pearson correlation coefficient (r)	p
	BMI	0.458	0.032
	E	-0.464	0.03
	E' lat	-0.659	0.002
	A' lat	0.445	0.049
	E' med	-0.816	<0.001
	2D GLS	0.571	0.006
	3D EF	-0.441	0.04

Legend: 3D GLS, three-dimensional global longitudinal strain; BMI, body mass index; E, peak E velocity; E' lat, peak E' velocity of lateral mitral annulus; E' med, peak E' velocity of medial mitral annulus; 2D GLS, two-dimensional global longitudinal strain; 3D EF, three-dimensional ejection fraction.

A linear regression analyses was performed to identify independent association of 3D GLS as dependent variable using as covariates different echocardiographic and clinical parameters. By these analyses 3D GLS was independently associated with E' med, E' lat and 2D GLS, adjusted value of R square coefficient showing that 76% of the 3D GLS variability can be predicted by the variation of the independent variables included in the model (Table IV).

Table IV. Linear regression analysis

Dependent variable	Covariate	ß	P	Adjusted R Square	Standard Error
3D GLS	**E' lat**	-0,321	0,040	0,769	3,073%
	E' med	-0,475	0,001		
	2D GLS	0,322	0,032		

Legend: 3D GLS, three-dimensional global longitudinal strain; E' lat, peak E' velocity of lateral mitral annulus; E' med, peak E' velocity of medial mitral annulus; 2D GLS, two-dimensional global longitudinal strain.

DISCUSSION

The results of the present study demonstrate that (i) there was a strong negative correlation between 3D GLS (systolic parameter of the LV function) and E'med (diastolic parameter of the LV function, (ii) there was a significant positive correlations between 2D GLS and IVST, PWT (concentric hypertrophy of the LV) and (iii) 3D GLS was independently associated with E' med, E' lat and 2D GLS, 76% of the 3D GLS variability could be predicted by the variation of these independent variables included in the model.

In literature we found that Galderisi M at al. in a previous study demonstrated a correlation of 2D GLS (measured by Speckle tracking method) with LV diastolic function (E/E') regardless of degree of LV hypertrophy [26]. In our study diastolic function was not complete evaluated, tissue Doppler velocities of mitral annulus being a raw estimation of LV diastolic function. However, in accordance with Galderisi studies [25-26] we found a negative correlation between 3D GLS and E'med (our parameter of diastolic function).

DÁndreea et al. studied the effects of different effort training protocols on LV strain indices. They showed no differences of 2D GLS between endurance and strength athletes. Also they demonstrated a positive association between E'lat, E'med and LVEDV ($p<0.001$) and an independent correlation between 2D GLS and sum of LV wall thickness ($p<0.005$) [27]. In our study we also found a significant correlation of 2D GLS with IVST ($p=0.035$) and PWT ($p=0.002$). This correlation is a practical demonstration of the influence exerted from physiologic LV hypertrophy on systolic function of the athlete's heart. On the other hand, in hypertensive patients with pathological LV hypertrophy, GLS has been shown to correlate negatively with the magnitude of LV hypertrophy [26].

More recent studies, which analyzed contribution of LV strain components in myocardial function at rest, in endurance athletes using 3D STE, showed that sinus bradycardia and LV mass are independent determinants of 3D GLS at rest [28-29]. Our study revealed that diastolic function (E' med and E' lat) and also 2D GLS was independent predictors of 3D GLS at rest in our team of rugby players.

Limitations

The entire group included in the analysis had only 26 athletes, so the results can be biased by the small number of participants to the study. Furthermore, we can not extrapolate these results to the entire population of rugby athletes, because we already know that the study group is not representative.

The difference of 24% of the variability of the 3D GLS variable could be explained by the existence of other predictor factors not investigated in our study.

Another limitation is the lack of quantification of other strain parameters like global circumferential or radial strain or LV twisting and torsion. Some of this measurement was obtained but could not be analyzed (inadequate quality echocardiography images).

CONCLUSIONS

The strain evaluation of our athlete's left ventricle using 2D STE revealed the fact that the higher the physiological hypertrophy of the left ventricle, the more increased longitudinal systolic function, in opposite with hypertensive patients with pathological LV hypertrophy, where 2D GLS was found significantly decreased.

3D STE is a new and feasible technique for assessing LV myocardial deformation in athletes. 3D GLS (a systolic parameter of the LV function) correlated both with a LV diastolic function parameter and another systolic parameter measured by 2D method (2D GLS), emerging as independent predictors of rugby players' longitudinal myocardial deformation at rest.

REFERENCES

1. Baggish AL, Yared K, Wang F, et al. The impact of endurance exercise training on left ventricular systolic mechanics. *Am J Physiol Heart Circ Physiol* 2008;295:H1109-16.
2. Butz T, van Buuren F, Melwig KP, et al. Two-dimensional strain analysis of the global and regional myocardial function for the differentiation of pathologic and physiologic left ventricular hypertrophy: a study in athletes and in patients with

hypertrophic cardiomyopathy. *Int J Cardiovasc Imaging* 2011;27:91-100.
3. Stefani L, Pedrizzetti G, De Luca A, et al. Real-time evaluation of longitudinal peak systolic strain (speckle tracking measurement) in left and right ventricles of athletes. *Cardiovasc Ultrasound* 2009;7:17.
4. Vitarelli A, Capotosto L, Placanica G, et al. Comprehensive assessment of biventricular function and aortic stiffness in athletes with different forms of training by three-dimensional echocardiography and strain imaging. *Eur Heart J Cardiovasc Imaging* 2013;14(10);1013-20.
5. Fagard RH. Impact of different sports and training on cardiac structure and function. *Cardiol Clin* 1997;15:397-412
6. D'Ándreea A, Galderisi M, Sciomer S, et al. Echocardiographic evaluation of the athlete's heart: from morphological adaptation to myocardial function. *G Ital Cardiol* 2009;10:533-44.
7. Galderisi M, Lomoriello VS, Santoro A, et al. Differences of myocardial sysstolic deformation and correlates of diastolic function in competitive rowers and young hypertensives: a speckle tracking echocardiography study. *J Am Soc Echocardiogr* 2010;23:1190-8.
8. Simsek Z, Hakan Tas M, Degirmenci H, et al. Speckle tracking echocardiographic analysis of left ventricular systolic and diastolic functions of young elite athletes with eccentric and concentric type of cardiac remodeling. *Echocardiography* 2013;30:1202-8.
9. Santoro A, Alvino F, Antonelli G, et al. Endurance and strenght athlete's heart analysis of miocardial deformation by speckle tracking echocardiography. *J Cardiovasc Ultrasound* 2014:22;196-204.
10. Caselli S, Montesanti D, Autore C, et al. Patterns of left ventricular longitudinal strain and strain rate in Olympic athletes. *J Am Soc Echocardiogr* 2015:28;245-53.
11. Szauder I, Kovacs A, Pavlik G. Comparison of left ventricular mechanics in runners versus bodybuilders using speckle tracking echocardiography. *Cardiovasc Ultrasound* 2015:18;13-7.
12. Stefani L, De Luca A, Toncelli L, et al. 3D strain helps relating LV function to LV and structure in athletes. *Cardiovasc Ultrasound* 2014; 14:33.
13. Monti IP, Mangiafico S, Buccheri S, et al. Myocardial deformational adaptations to different forms of training: a real-time three-dimensional speckle tracking echocardiographyc study. *Heart Vessels* 2015:30;386-95.
14. Du Bois. Du Bois. Arch Intern Med 1916;17:863-71.
15. Lang RM, Biering M, Devereux RB, et al. Recommendation for chamber quantification. *Eur J Echocardiogr* 2006;7:79-108
16. Devereaux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy:comparison to necropsy findings. *Am J Cardiol* 1986;57:450-8.
17. Schiller NB, Shah PM, Crawford M, et al. Recommendation for quantification of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989;2:358-67.
18. Galderisi M, Henein MY, D'hooge J, et al. On behalf of the European Association of Echocardiography. Recommendation of the European Association of Echocardiography: How to use echo-Doppler in clinical trials: different modalities for different purposes. *Eur J Echocardiogr* 2011;12:339-53.
19. Olsen NT, Jons C, Fritz-Hansen T, et al. Pulsed-wave tissue Doppler and color tissue Doppler echocardiography: calibration with M-mode, agreement and reproducibility in a clinical setting. *Echocardiography* 2009;26:638-44.
20. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two dimensional echocardiography. *Am Heart J* 1984;128:301-7.
21. Korinek J, Kjaergaard J, Sengupta PP, et al. High spatial resolution speckle tracking improves accuracy of 2-dimensional strain measurements: an update on a new method in functional echocardiography. *J Am Soc Echocardiogr* 2007;20:165-70.
22. Dalen H, Thorstensen A, Aase SA, et al. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT study in Norway. *Eur J Echocardiogr* 2010;11:176-83.
23. Muraru D, Badano LP, Piccolo G, et al. Validation of a novel automatic border detection algorithm for rapid and accurate quantitation of left ventricular volumes based on Three-dimensional echocardiography. *Eur J Echocardiogr* 2010;2:359-68.
24. Langeland S, Rabben SI, Heimdal A, et al. 4D Strain: validation of new 3D speckle tracking and left ventricular tool in simulated echocardiographic data. *Eur J Echocardiogr* 2010;11(suppl 2):Abstract P658.
25. Galderisi M, Esposito R, Schiano-Lomoriello V, et al. Correlates of global area strain in native hypertensive patients: a three-dimensional speckle-tracking echocardiography study. *Eur J Echocardiogr* 2012;13:730-38.
26. Galderisi M, Lomoriello VS, Santoro A, et al. Differences of myocardial systolic deformation and correlates of diastolic function in competitive rowers and young hypertensives: a speckle-tracking echocardiography study. *J Am Soc Echocardiogr*. 2010;23(11):1190-8.
27. D'Andrea A, Cocchia R, Riegler L, et al. Left ventricular myocardial velocities and deformation indexes in top-level athletes. *J Am Soc Echocardiogr*. 2010; 23(12):1281-8.
28. Lo Iudice F, Petitto M, Ferrone M, et al. Determinants of myocardial mechanics in top-level endurance athletes: three-dimensional speckle tracking evaluation. *Eur Heart J Cardiovasc Imaging* 2017;18:549-555.
29. D'Ascenzi F, Solari M, Mazzolai M, et al. Two-dimensional and three-dimensional left ventricular deformation analysis: a study in competitive athletes. *Int J Cardiovasc Imaging.* 2016;32(12):1697-1705.

EVALUAREA FUNCTIEI SISTOLICE A VENTRICULULUI STANG CU AJUTORUL METODELOR ECOCARDIOGRAFICE SPECKLE TRACKING BIDIMENSIONAL SI TRIDIMENSIONAL LA UN LOT DE SPORTIVI DE PERFORMANTA (JUCATORI DE RUGBY)

REZUMAT

Remodelarea adaptativa a cordului la sportivi apare ca urmare a modificarilor morfologice si functionale datorate protocoalelor de antrenament fizic intens.Studiile asupra deformarii ventriculului stang la sportivi sunt echivoce iar rezultatele sunt controversate. Scopul studiului nostru este evaluarea strainului sistolic al ventriculului stang la un lot de rugbysti folosind tehnici ecocardiografice noi (metoda speckle tracking bidimensionala respectiv tridimensionala). In acest scop am evaluat intreg lotul regional de rugby constand in 26 de sportivi si le-am efectuat masuratorile standard ecocardiografice bidimensional respectiv tridimensional. Am gasit corelatii pozitive semnificative statistic intre strainul longitudinal global bidimensional (2D GLS) si grosimea septului inerventricular si peretelui posterior al ventriculului stang ($p<0,05$, $r<0,75$) si corelatie negativa cu excursia inelului mitral respectiv tricuspidian ($p<0,05$) . Am gasit de asemenea o corelatie pozitiva semnificativa negativa intre strainul longitudinal global tridimensional (3D GLS) si indicele de masa corporala ($p = 0,032$), viteza A'lat a inelului mitral ($p = 0,049$), 2D GLS ($p = 0,006$) si o corelatie negativa cu viteza E a fluxului mitral ($p = 0,03$), E“lat si E ' med a inelului mitral ($p = 0,002$, respectiv $p <0,001$), fractia de ejectie 3D ($p = 0,04$), corelatia cea mai puternica fiind cu E' med ($p < 0,001$, $r = -0.816$). Prin analiza de regresie liniara, am aratat ca 76% din variabilitatea 3D GLS poate fi prezisă prin variația variabilelor independente incluse in model (E „med E“ lat și 2D GLS).

Concluzii: Ecocardiografia spekle tracking 2D și 3D sunt tehnici noi și fezabile pentru evaluarea deformarii miocardice a ventriculului stang la sportivi. Am ajuns la concluzia că sportivii cu cea mai mare hipertrofie fiziologică a ventriculului stang au avut cel mai crescut 2D GLS, spre deosebire de pacienții hipertensivi cu hipertrofie patologica de ventricul stang, unde 2D GLS a fost găsit mult scazut.

Cuvinte cheie: sportivi, ecografia speckle tracking, strain, functia sistolica a ventriculului stang