

# Syncope in Chronic Constitutional Hypotension: Gender based Retrospective observational study in symptomatic women

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Citation: Lagi A, Cencetti S (2017) Syncope in Chronic Constitutional Hypotension: Gender based Retrospective observational study in symptomatic women. J Clin Exp Res Cardiol 3(1): 101

Received Date: October 26, 2016 Accepted Date: January 13, 2017 Published Date: January 16, 2017

## Abstract

**Introduction:** The association between chronic constitutional hypotension (CCH) and symptoms is uncertain both as pathophysiological correlation as a statistical link. The study was undertaken in order to investigate the existence of a significant association between CCH and symptoms and identify the most represented ones.

**Methods:** Women only have been used because of the higher incidence of CCH in their sex. The symptoms considered were studied in three groups of subjects: A and B groups, identified for systolic arterial pressure (SAP) < 100 mmHg and diastolic blood pressure (DAP) < 60 mmHg, and finally a C group of control consisting of normotensive women. Symptoms considered were: dizziness, anxiety / or depression, asthenia and / or fatigue, transient loss of consciousness (TLC), accidental falls, and body mass index (BMI).

**Results:** Patients with CCH had significant incidence of anxiety / depression and asthenia / fatigue and TLC versus controls. Individuals with PAD < 60 mmHg (group B) had a significance statistical difference of events also vs. the group A.

**Discussion and conclusion:** The women with CCH are symptomatic and have a lower BMI than controls. The low value of PAD defines a major risk group for TLC and a worse prognosis.

**Keywords:** Syncope; Chronic hypotension; Hypotension; Chronic constitutional hypotension; Transient loss of consciousness

## Introduction

In the medical literature the Chronic Constitutional Hypotension (CCH) or idiopathic is defined for stable value of arterial pressure, less than 110/60 mmHg in men and 100/60 mmHg in women [1].

Everything is uncertain near hypotension. Its incidence varies between two sexes, lower in men (1.8%) than women (5.8%) and by age [1,2]. The link of CCH with the symptoms complained from patients is undefined. The most scientific consensus reports as random association, thereby denying the CCH one role as a disease [3,4].

The link between the CCH and symptoms is correlated to the systolic blood pressure, regardless of the diastolic as affirmed in an Australian study, where, between 20 and 30% of the population suffered from palpitations and feeling of empty head when the values of systolic arterial pressure were lower than 110 mmHg [5]. Finally, the cause - effect relationship between CCH and symptoms associated with is completely unresolved: whether they are cause or consequence or just related. The opinions of the authors are different and opposite.

The aim of the work is to establish a significant relationship between CCH and symptoms in order to determine which are the most represented in a population of female CCH.

## Methods

We choose to include in the study females for the higher incidence of CCH in their sex. The patients were recruited in a hospital outpatient clinic associated with a secondary referral centre for Internal Medicine. The sending of patients was due to the presence of symptoms. The selection took place for a period of 21 months, in the years 2013 - 2014. The patients were subjected to general medical examination and electrocardiogram. Blood pressure was measured while sitting, lying and standing after 3' minutes of standing. The patient was accepted after a second visit, after at least 30 days, which was to confirm the first measurement values. A semiautomatic device setup to deflate and inflate the cuff automatically at one minute intervals was used. Values were obtained

by oscillometry and displayed digitally. It was calculated by the average value of three measurements, each one always less than the cut-off established. The measurement was performed on the right arm.

As a result of the measurements we proceeded to the classification into three groups by the value of the arterial pressure:

- 1) Systolic blood pressure (SAP) < 100 mmHg: group A
- 2) Diastolic blood pressure (DAP) < 60 mmHg: Group B
- 3) Blood pressure (AP) > 110/60 and < 140/90 mmHg: group C

Have been investigated and have been reason for exclusion from the study:

- Taking drugs lowering AP (diuretics,  $\alpha$  or  $\beta$ - blockers and calcium channels blockers, ACEi, ARB)
- Latest hypovolemic diseases (major bleeding, vomiting and / or diarrhoea)
- Pregnancy
- Latest prolonged immobilization
- Orthostatic and/or post- prandial hypotension
- Heart disease

The symptoms which developed the survey were chosen because they are normally related to chronic hypotension:

- Asthenia and fatigue were defined as progressive development on performing the daily activities. Was initially asked the patient "Within the last month have you suffered from any problems with always feeling tired?" At the affirmative answer asthenia was considered present if the patient was able to perform all its usual occupations, from work to fun, but with a mental and physical effort. The effort was diagnosed when the patient had to give up doing something because too tired to start it or finish it.
- Dizziness, defined as light-headedness and / or vertigo and / or dizziness and / or inability to concentrate.
- Anxiety and/or depression were diagnosed as prolonged use of anti-anxiety drugs or antidepressants. Diagnoses have been accepted whether they were made before and during the period of enrolment.
- Transient loss of consciousness (TLC) medical history compatible with vasovagal syncope with a frequency greater than twice in a lifetime.
- Accidental falls.
- Body mass index was calculated according to functional the formula: weight (kg) / height (cm<sup>2</sup>).

A comparable group of normotensive females of the same age was chosen as a control (Table 1).

Due to relevance of medical history data present in the data collection all subjects were assessed for cognitive function, subjecting them to specific test according to Broadbent. Were included in the study subjects with less than 45 points [6,7].

Local Ethical Committee approved the study (Ref:37/2014).

	A group: SAP < 100 mmHg	B group: DAP < 60 mmHg	C group: AP > 100/60 mmHg	P
Number of patients	58	47	68	
Mean age	52	52	52	
< 45 years	29	22	35	ns
> 45 years	29	25	33	ns
BMI	18	19	23	<0.01
Mean AP mmHg	89	57	121/70	
Diabetes	3 (5%)	2 (4%)	3 (4%)	ns
Smoking	14 (24%)	11 (23%)	16 (23%)	ns
Alcohol*	2 (3%)	1 (2%)	2 (3%)	ns
Prior Pregnancy	19 (33%)	16 (34%)	23 (34%)	ns
Exercise^	6 (10%)	6 (13%)	8 (12%)	ns

\*More than 3/4 litres wine    ^ more than 20 minutes /die  
SAP, DAP & AP: Systolic, Diastolic and Arterial Pressure

**Table 1:** Characteristics of the population study

## Statistical Analysis

The statistical analysis was referring to the two study groups (groups A and B) and conducted for comparison with the control group (group C).

Baseline demographics and hemodynamic indices were compared between groups using an analysis of variance for continuous data (ANOVA) and the  $\chi^2$  test for categorical data. Comparisons were made between patients and controls.  $p < 0.05$  was significant considered.

## Results

We examined 3986 patients with a mean age of 71 years, range 18-81 years, of which 48% were women. Among these 1913 patients, 6.1% (116 pts) met the selection criteria. Based on the cognitive test selection, 19 patients with score  $> 45$  were excluded [6]. So 97 patients were recruited, 8 of whom had both selection criteria with a cut off of SAP  $< 100$  and DAP  $< 60$  mmHg so they were included in both groups of study for a total of 105 cases. The average age of patients was 52  $\pm$  22 years and 57% were aged less than 45 years. No difference in lifestyle habits is registered between the two study groups and the controls (Table 1).

Both CCH groups, both A and B, show a total number of symptoms per patient more than controls: 2 and 2.7 / patient compared to the value of 1.04 / patient of controls. The individual symptoms show significant differences from controls vs A and B for the asthenia ( $p < 0.05$  and 0.001) while the fatigue and anxiety/ depression is significant only in the group B vs C ( $p < 0.05$ ).

The individual symptoms show significant differences for TLC both B group vs. C ( $p < 0.0005$ ) and B vs C ( $p < 0.001$ ) (Table 2). The TLC affects more in age  $< 45$  years (Table 3). Significant inverse correlation between age and TLC was found (OR =0.95 CI 95%: 0.91 - 0.97). There are no differences for the dizziness and accidental falls. In group B, also in cases in which there are no statistical differences vs. the group A, the percentages of incidence of the symptoms is higher than in group A. (Table 2).

	Group A	%	Group B	%	p1	Group C	%	p	p2
Number of patients	58		47			68			
Dizziness	15	25	18	38	NS ( $> 0.2$ )	23	34	NS ( $> 0.2$ )	NS ( $> 0.2$ )
Asthenia	25	43	26	55	NS ( $> 0.2$ )	10	15	$< 0.0005$	$< 0.001$
Fatigue	8	14	15	32	$< 0.05$	4	6	NS ( $> 0.2$ )	$< 0.001$
TLC	22	38	19	40	NS ( $> 0.2$ )	7	10	$< 0.001$	$< 0.0005$
Falls	6	10	9	19	NS ( $> 0.2$ )	7	10	NS ( $> 0.2$ )	NS ( $> 0.2$ )
Anxiety/depression	23	39	27	57	NS ( $< 0.1$ )	19	28	NS ( $> 0.2$ )	$< 0.05$
Symptoms/patient	2		2.7			1.04			

p = group C vs A; p1= group B vs A; p2= group C vs B

**Table 2:** Associated symptoms to Chronic Constitutional hypotension

	Group A		Group B		Total	
Total TLC	22 (38%)		19 (40%)		41 (39%)	
$< 45$ yo	13	60%	14	74%		66%
$> 45$ yo	9	40%	5	16%		34%

**Table 3:** Relationship between Transient Loss of Consciousness and age

## Discussion

The decision to limit the cases to the female sex has been made in order to make it as homogeneous as possible the cases, in question that the CCH of women is different from that of men. The study has had the retrospective character as the appearance of the vagal syncope is occasional, rare and then it seemed too long to program an appropriate prospective period of observation to collect an adequate number of TLC.

The aim of the work was to demonstrate that a group of patients suffering of CCH was symptomatic and define the most represented symptoms compared to a control group. The use of strict criteria for exclusion and inclusion has extended the selection of patients that lasted for 21 months. The benefit was to be able to refer to a selected population. In particular, it is sure that the women included in the study are all CCH. Cardiac diseases were excluded while have not appeared signs or symptoms of endocrine disorders, in particular for myxoedema and primitive or secondary adrenocortical failure.

The first statement that results from this study is that hypotensive women, however it appreciates the cut-off value for the SBP or DBP or both, have symptoms. The data is conform to the existing literature but our results descend from a dedicated study, albeit retrospectively, so that the strength of our assertion certainly looks stronger. Another finding is that the incidence of women with CCH is equal to 6.1% of women who belong to a clinic for Internal Medicine, as a secondary reference centre. The comparison data in the literature refers to the General Medicine and appears to infer the value of 10% which refers to the people of both sexes [3]. The simplest interpretation is that the associated symptoms related to hypotension are not considered by either the patient or the doctor as symptoms or signs of imminent danger and therefore amenable to intervention or non-intervention deferrable for a recommendation to a specialist referral. Also one must consider that often we neglect or ignore that there are centres or facilities

dedicated to the study and treatment of low blood pressure, so no wonder that a secondary centre of Internal Medicine can be a vantage point not attended a first-level clinic.

In reference to the symptoms associated with the CCH it should be noted how numerous, such as to be in association. The number of symptoms/patient relationship varies from 2.7 in group B to 2 in Group A up to 1.04 in controls. The sense of this report indicates a possible correlation between abundance of symptoms and blood pressure level.

Difference between the subjects of group B vs. those of group A was also detected because in the first there is a statistical significance of symptoms vs. those of group A that distinguishes itself instead only for the TLC and asthenia.

This figure would assume that the characteristics of the group B, the PAD below 60 mmHg, are a significant clinical marker for the presence of symptoms.

Each of the symptoms considered has its peculiarities:

- **Dizziness:** it is a generic term that includes many elements (light-headedness and/or dizziness and/or inability to concentrate) used to express a form of physical and psychological discomfort. It looks much represented inside the study population and in the controls due to many clinical pictures enclosed into the dizziness. This explains the lack of statistical significance.
- **Asthenia and fatigue** have disabling symptoms that affect not only the well-being but also on daily activities involving work and recreational activities. Between the two symptoms exists only a difference of intensity. The fatigue, which is the true disabling symptom, distinguishes between controls and group of CCH with PAD below 60 mmHg, and then providing elements to a clinical correlation (Table 2).

Asthenia is significantly represented in both study groups (A and B) to its low detection threshold, but taken together with fatigue the two symptoms affect a high proportion of subjects contributing in a major way to the feeling of unease of these patients. In literature is reported relation between systolic blood pressure and tiredness in both men and women [8]. The symptoms are detected with an average of 30% of the cases studied, 42% for hypotensive women with SBP < 100 to 28% of those with SAP > 110. Our analysis distinguished between asthenia and fatigue detecting the first in 43 and 55% versus 15% of controls, and the second in 14 and 32% compared with 6% of controls. The distinction between asthenia and fatigue observation gives greater strength because it shows the same tendency in both symptoms and not the influence of age, thus leaving to the pressure its primary responsibility as a strong signal of association even if of uncertain causality.

- **Fainting** is anecdotally considered to be linked to either extreme of blood pressure. This happens especially in hypotensive women towards men with a difference between subjects with SAP < 100 and > 100 mmHg, 12.8% vs 8.9% [5].

The relation between fainting and age seemed to be U-shaped, with the greatest risk in the youngest and the oldest subjects. In our data there is significant difference in the incidence of syncope in relation to age, which makes this class different subjects from the population of those who suffer because of cardiogenic syncope or cause reflected. The incidence of fainting, is recorded in 38 and in 40% of cases in group A and B, respectively, with no difference between groups but with high statistical significance ( $p < 0.001$  and  $< 0.0005$ ) both A and B than in controls. The data therefore confirms the association between systolic and diastolic blood pressure with syncope and appears to identify the PAD less than 60 mmHg as a particular clinical feature. Conversely, accidental falls, when cases with TLC are extracted, do not show differences. Certainly, the diagnosis was made possible from the age of juvenile cases and the cooperation offered by a good cognitive condition of the participants.

- **Anxiety and depression:** it is difficult to dissociate these two symptoms, and also both from fatigue and exhaustion. We have chosen to define this symptomatic category with the use of anti-anxiety drugs or antidepressants. We have thus adopted an easy selection criterion.

There is no reference to the literature on the association between psychiatric symptoms and hypotension, and our data represent a first in this sector. Thus we have found a high incidence of the association as in the studied groups than in controls: 39 and 57% versus 28% of controls. The statistical difference, however, is weak and only for the group with PAD below 60 mmHg compared to controls ( $p < 0.05$ ) and no difference of the controls vs. the group A or between group A and B. This data makes weak the association between anxiety and depression with CCH. The scenario is similar to that which is found to asthenia and fatigue, possibly suggesting an association between these two categories of symptoms.

Finally, another figure emerges with force, what the symptomatic hypotension is associated with a BMI value significantly lower both in respect of general population (normal BMI 24) that of controls (Table 1), confirming the concept that CCH is probably a disease in which most parts are genetically determined.

## Conclusion

This work represents a breakthrough in the field of hypotension and because it refers to women only is because it was built with the intent to test the association with different symptoms usually attributed to chronic arterial hypotension. The scope of work was to demonstrate the significant incidence of syncope in hypotensive women. Data exists with high statistical significance, although

based on the medical history data. It emerges with statistical power that the PAD < 60 mmHg select a group of hypotensive women within the group of subjects affected from CCH with more frequent and more pronounced symptoms, so that they can be considered the most serious. The study of pathophysiological correlations between the low blood pressure and symptoms is not within the aim of the work.

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