Ann Ist Super Sanità 2013 | Vol. 49, No. 3: 309-312
DOI 10.4415/ANN_13_03_13

Cugini's syndrome: its clinical history and diagnosis

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Abstract

Introduction. This article deals with the description and diagnosis of a new nosographic syndrome, which received the eponym of "Cugini's syndrome" by the name of the Author who discovered its clinical picture. This syndrome is characterized by the binomial: "minimal target organ damage associated to monitoring prehypertension".

Clinical history and diagnosis. Between the years 1997 and 2002, the Author published a series of investigations regarding some office normotensives who inexplicably showed incipient signs of target organ damage (TOD). Investigated via ambulatory (A) blood (B) pressure (P) monitoring (M), these subjects were surprisingly found not to be hypertensive. Neverthless, the office normotensives with TOD exibited the daily mean level of their systolic (S) and diastolic (D) BP ($DML_{SBP/DBP}$) significantly more elevated as compared to true normotensives. Because of these ABPM findings, the Author realized that the investigated subjects were false normotensives whose TOD was associated with a monitoring prehypertension (ABPM-diagnosable prehypertension *alias* monitoring prehypertension *alias* masked prehypertension). The year after the last Cugini's investigation, the INC-7 Reports introduced the term: "prehypertension" in its classification of arterial hypertension, as an office sphygmomanometric condition in between office normotension and office hypertension. The ABPM cut-off upper limits for a differential diagnosis between monitoring normotension, prehypertension and hypertension are reported, as calculated by the Author in its collection of ABPMs. The eponym of "Cugini's syndrome" was assigned in 2007 and confirmed in 2009.

Conclusive remarks. The monitoring prehypertension is a further condition of discrepancy between office sphygmomanometry and ABPM, as per a masked prehypertension, whose diagnosis has to be immediately diagnosed, for preventing the onset of a TOD. There are reported the present investigations dealing with the possible need for an early antihypertensive treatment of prehypertension. A pharmacological treatment seems to be especially justified in the presence of a Cugini's syndrome.

Key words
- blood pressure
- ABPM
- ABPM-diagnosable prehypertension
- monitoring prehypertension
- masked prehypertension
- normotension
- hypertension

CLINICAL HISTORY

The so called "Cugini's syndrome" (CS) is a clinical picture characterized by the binomial "target organ damage/monitoring prehypertension".

Its identification was made by the physician Pietro Cugini (Rome, 1936), Professor of Internal Medicine at the Sapienza University of Rome (Italy), via a series of clinical researches, performed between 1997-2002 [1-7], in office normotensive subjects showing initial and minimal (say, incipient) signs of tensive target organ damage (TOD).

The eponym was conferred in 2007 [8] and restated in 2009 [9] by a panel of international leading experts of biometric standardization and clinical management of the ambulatory (A) blood (B) pressure (P) monitoring (M), for the diagnostic differentiation between normotension and hypertension.

The eponymic attribution was motivated by the fact that Cugini's studies documented, via ABPM, the existence of office normotensives with initial signs of TOD who were found to be neither normotensives nor hypertensives.

As a matter of fact, they were found to show a statistically significant elevation of the daily mean level of their systolic (S) and diastolic (D) BP values ($DML_{SBP/DBP}$), in between the $DML_{SBP/DBP}$ detectable in true normotensives and true hypertensives.

To describe this unsuspected intermediate BP regimen, the he thought to use the term: "prehypertesion" as a indicative of ABPM-diagnosable prehypertension *alias* monitoring prehypertension *alias* masked prehypertension.

Interestingly, one year after the Cugini's last publication, the word "prehypertension" made its appearance in the international classification, still in use, proposed by the VII Report of the Joint National Committee on

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Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in 2003 [10] and restated in 2004 [11]. For the sake of history, it must be stressed that at the time of his researches, the Author was involved in an international study, called "From Womb to Tomb" (FWTT), promulgated by Prof. Franz Halberg and coworkers at the Chronobiology Laboratories of Minnesota University (Minneapolis, USA). This study was dealing with the standardization of time-qualified reference limits for the within-day BP values in clinically healthy humans, from birth to death [12-15].

Because of this involvement, his laboratory of Clinical Chronobiology at the Policlinico Umberto I of Sapienza University of Rome, was equipped with automated, wearable, non-invasive BP monitors, fulfilling the acceptance criteria of AAMI (Association for the Advancement of Medical Instrumentation) and BHS (British Hypertension Society).

Importantly, in collecting true normotensives reliable for the FWTT study, in its quality of clinician, he had the chance to observe some office normotensive adults who were showing incipient signs of TOD, namely, a first stage hypertensive retinopathy [1, 2]. He immediately suspected that these individuals could be affected by an "odd hour hypertension", including the non-dipping phenomenon.

Because of this reasonable hypothesis, all these subjects were examined, via ABPM, in their 24-h BP pattern.

Interestingly and surprisingly, he could ascertain that none of these subjects exhibited intradiem systolic (S) and diastolic (D) DBP values higher than the pertaining day-night upper reference limits, even though, they were showing a more elevated profile of their 24-h BP values.

Because of this unexpected finding, he realized that the office normotensive subjects with an incipient TOD could be regarded as *putative normotensives*.

For coherence with this plausible hypothesis, he decided to perform a statistical comparison of the daily mean level of monitored systolic (S) and diastolic (D) BP values ($DML_{SBP/DBP}$), as estimated in true normotensives and putative normotensives.

Accordingly, from his ABPM database, he extracted a sample of true monitoring normotensives, matching by age, sex and anthropometric characteristics with the group of putative normotensives with incipient TOD, namely a first stage of hypertensive retinopathy.

Surprisingly, the statistical analysis revealed that notwithstanding the lack of supranormal BP values, the putative normotensives exhibited a significant elevation of their $DML_{SBP/DBP}$ as compared to the true monitoring normotensives *(Table 1)*. At this point, having already excluded that the office normotensives with retinal TOD had other factors of cardiovascular risk, he thought that the office normotensives with a TOD subjects could be really regarded as *false normotensives*.

Because of this hypothesis, he thought to discover whether or not the finding of a significantly more elevated $DML_{SBP/DBP}$ could be observed in office normotensives with *other incipient TODs*.

The new TODs investigated in office normotensives were: 1) interventricular septum hypertrophy; 2) interventricular septum hypertrophy of the novel transplanted heart; 3) endothelial dysfunction; 4) gestational impairment of blood flow in uterine arterioles; 5) gestational intrauterine retardation of fetal growth, by preliminarily excluding that there were operative other risk factors for TODs [3, 7].

Importantly, the biometric examination gave a confirmation to his hypothesis in that all the putative normotensives with various TODs were found to show a statistically significant elevation of their $DML_{SBP/DBP}$, in absence of intradiem BP values higher than normal.

Because of these homogenous results, he realized that it was plausible to think about an enlarged syndrome, to be named "tensive target organ damage/monitoring prehypertension syndrome".

Table 1

Number of supranormal intradiem systolic (S) and diastolic (D) blood pressure (BP) values as well as daily mean levels of SBP and DBP along with the results of their statistical contrasts in true normotensive and putatives normotensives with initial signs of hypertensive retinopathy. Reproduced from the *Journal of the Siena Academy of Sciences* (*JSAS* 2012;4:12-21) with the permission of Accademia dei Fisiocritici of Siena, Italy

Selected parameters at the ABPM	Pressurometric variables	Group A True normotensives	Group B Putative normotensive with initial signs of hypertensive retinopathy	Statistical contrasts (A *vs* B)
Within-day values above 135 mmHg (day-time)/85 mmHg (night-time)	SBP	0	0	χ^2 test NA
	DBP	0	0	NA
DML (mmHg/24-h)	SBP	112 ± 4	23 ± 3	Student *t* test (*p* value) < 0.001
	DBP	72 ± 2	78 ± 2	< 0.01

ABPM: ambulatory blood pressure monitoring; SBP: systolic blood pressure; DBP: diastolic blood pressure; DML: daily mean level given as mean ± standard error of the mean; NA: not applicable.

Table 2
Cugini's criteria, presumably applicable to the ABPM, for a *tripartite* diagnostic differentiation among monitoring normotension, prehypertension and hypertension. Reproduced from the *Journal of the Siena Academy of Sciences* (*JSAS* 2012;4:12-21) with the permission of Accademia dei Fisiocritici of Siena, Italy

Monitoring blood pressure regimen	Supranormal day-night values of SBP and DBP (mmHg)	Daily mean level of SBP and DBP $DML_{(SBP/DBP)}$ (mmHg/24-h)
Normotension	**None** > 135/85 (day-time) and > 125/75 (night-time)	105-120/75-80
Prehypertension	**None** > 135/85 (day-time) and > 125/75 (night-time)	121-130/81-85
Cugini's syndrome	IDEM	IDEM + initial signs of TODs
Hypertension	**At least 20%** > 135/85 (day-time) and > 125/75 (night-time)	≥ 131/86*

SBP: systolic blood pressure; DBP: diastolic blood pressure.
*Monitoring hypertension may not show a higher $DML_{(SBP/DBP)}$ whether the 24-h blood pressure profile shows an almost comparable number of supranormal and subnormal values.

DIAGNOSTIC CRITERIA

It is important to remark that the term "prehypertension" of the JNC-7 Report merely refers to the office sphygmomanometry of BP.

Because of this, he analyzed the ABPM data base for determining the cut off limits to be adopted for the tripartite ABPM-mediated diagnosis of normotension, prehypertension (including the CS), and hypertension *(Table 2)*.

The last problem faced by Cugini was the attempt to estimate the prevalence of monitoring prehypertension as well as of his syndrome by revisioning his ABPM data base. From his personal data, it has been derived that the monitoring prehypertension can be found in 3-5% of subjects with office normotension, while the prevalence of a monitoring prehypertension associated with TODs, namely a CS, account for about 10% of the monitoring prehypertensives.

It important to restate that all the above-cited biometric and epidemiological estimates have been derived from a personal ABPM data base. Therefore, it remains clear that further epidemiological and pharmacological investigations are needed in order to better define: 1) the cut off limits for an indisputably differentiating monitoring normotension, prehypertension and hypertension via ABPM; 2) the clinical course of prehypertension and CS in terms of outcomes; 3) the effective impact on health care; 4) the real necessity of a drug treatment, according to the standards of Evidence Based Medicine.

CONCLUSIVE REMARKS

It is important to stress that in JNC-7 the term "prehypertension" is intended as a potential condition of risk (pre-disease) for a possible future development of hypertension. As a matter of fact, the JNC-7 only suggests a non-pharmacological intervention for correcting the modifiable factors of cardiovascular risk. Looking as the CS, it seems that the ABPM-diagnosable prehypertension is an actual hemodynamic regimen per se responsible for a cardiovascular damage. This clinical observation lead Cugini to hypothesize the need of a drug treatment of arterial prehypertension by recurring to *ad hoc* studies (drug *vs* placebo and/or alternative measures, such as changes in lifestyles), according to the standards of Evidence Based Medicine. The reliability of this suggestion seems to have a confirmation by some ad hoc studies, initiated five years later his retirement [16-25].

As a further consideration, it must be remarked that before the identification of the monitoring prehypertension, the clinical combination of a TOD with an office normotension remained nosographycally undiagnosable.

In fact, in 2002 Pickering *et al.* [26] compiled a four item diagnostic vademecum with relation to the concordance/discordance between office sphygmomanometry (OS) and ABPM, *i.e.*, 1) normotensives at OS and ABPM *alias* true normotensives; 2) hypertensives at OS and ABPM *alias* true hypertensives; 3) hypentensives a t OS, normotensives at ABPM *alias* white coat hypertensives; 4) normotensives at OS, hypertensives at ABPM *alias* masked hypertensives. Thus, the masked prehypertension proposed by him, results to be a fifth diagnostic category, *i.e.*, normotensives at OS, monitoring prehypertensives at ABPM *alias* masked prehypertensives, potentially prone to develop end organ damage as per a CS. This new clinical evidence may be of substantial relevance, *e.g.*, for the revision of guidelines.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

Received on 13 March 2013.
Accepted on 22 May 2013.

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