"TENSIVE TARGET ORGAN DAMAGE/MONITORING PREHYPERTENSION SYNDROME", ALIAS CUGINI'S SYNDROME, AS NARRATED BY THE AUTHOR

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Abstract. This is the tale in first person of how I discovered the "Tensive target organ damage/Monitoring prehypertension syndrome", which received an acknowledgement of paternity with the nosographic eponym of "Cugini's syndrome". The presentation is made with the intention of showing how the *research methodology* and *clinical reasoning* can act as an *epistemological guide*, primarily in detecting and, secondarily in defining such a syndromic picture. I will narrate, in an anecdotal way, the history of this syndrome that has origin in 1980 when I received the invitation to approach, as Visiting Professor, the Chronobiology Laboratories of Minnesota University, directly from their legendary Chief, Prof. Franz Halberg, the Founder of the discipline "Chronobiology". As an invited participant to an international project of research named: "International Womb-to-Tomb Chronome Initiative", devoted to standardize the time-qualified reference limits of blood pressure from neonatal to old age, I could use the first available equipments (Pressurometers) for executing the Ambulatory Blood Pressure Monitoring. Accordingly, I started to collect the ABPM of a large sample size of clinically healthy subjects. Collection continued going back and forth between Italy and USA. In this activity of recruitment for creating a database of true normotensives and true hypertensives, I had the chance to meet some *office normotensives* who inexplicably showed *initial signs of hypertensive retinopathy,* a sign of "Target Organ Damage" (TOD), while, unexpectedly, were showing *no supranormal BP values* at the ABPM. In order to explain the retinal TOD, I suspected that they were true non-hypertensives but not true normotensives (presumably normotensives *alias* putative normotensives). Therefore, I compared the Daily Mean Level of their 24-h systolic (S) and diastolic (D) BP values [$DML_{(SBP/DBP)}$] with the analogous estimate of the true normotensives. With surprise I could see that the retinopathic putative normotensives, despite the lack of surpranormal at the ABPM, had their $DML_{(SBP/DBP)}$ significantly increased, just in between true normotension and true hypertension. It was the year 1997, when I called this intermediate BP regimen: "ABPM-diagnosable prehypertension", *alias* "monitoring prehypertension", *alias* "pressurometric prehypertension", *alias* "masked prehypertension", and described the "Minimal-change hypertensive retinopathy/monitoring prehypertension syndrome". The association of a minimal tensive TOD with a monitoring prehypertension in office normotensives received a confirmatory certainty in other consecutive investigations, performed by me from 1997 to 2002, dealing with minimal signs respectively of: 1. interventricular septum hypertrophy in native hearts, 2. interventricular septum hypertrophy in novel transplanted hearts, 3. gestational impaired blood flow uterine arteries, 4. intrauterine growth retardation, 5. endothelial dysfunction. In all these clinical pictures, I could demonstrate that the initial tensive TOD was associated to a significant elevation of $DML_{(SBP/DBP)}$ just in between normotension and hypertension as per a *monitoring prehypertension*. Accordingly, I enlarged the appellative of the syndromic picture in "Minimal signs of TOD/monitoring prehypertension", *alias* "Tensive target organ damage/Monitoring prehypertension". Importantly, in 2007 and 2009 this clinical association has been eponimically called: "Cugini's syndrome" in an international context.

Key words: Monitoring normotension; monitoring prehypertension; masked prehypertension; ABPM; Target Organ Damage; End-Organ Damage; Cugini's syndrome.

THE HUMAN ASPECTS OF THIS HISTORY

The unexpected encounter

The history of the syndromic association: "Tensive target organ damage/Monitoring prehypertension syndrome", named with the eponym of "Cugini's syndrome", has origin in 1980 when I have been invited, as Visiting Professor, to attend the Chronobiology Laboratories of Minnesota University (USA) by their Director in person, Prof. Franz Halberg, the Founder of the biomedical discipline called "Chronobiology.

Why this prestigious invitation? Because I had the chance to meet Franz Halberg in a very singular circumstance that completely changed my life of medical researcher. In 1979, I was attending in Parma at a Congress on Hypertension in Children and Adolescents, where I had a presentation [1].

After my lecture, the loudspeaker announced:

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– Professor Cugini, please contact the Congress Secretariat for a very urgent information.
– Thinking to a bad surprise, I immediately went to the Congress Office. When arrived, the hostes told me:
– Professor, in that room over there, Professor Halberg is waiting for you.
– What did you say? Professor Franz Halberg?
– Yes, Professor Halberg from Minnesota University.

I was shocked hearing that the Father of Chronobiology, candidate to the Nobel Price, Author of Cosinor Method [2, 3] as well as of the Chronobiological Glossary [4], asked for me. With a motivated curiosity, I get into the room, finding waiting a middle-age gentleman who, with a simple gesture, gave me his right hand, saying:

– May I introduce myself? Franz Halberg from Minnesota University. Nice to meet you.

In shaking his hand, I said:

– It is a great privilege and honour for me to know you personally.

Soon after these civilities, Professor Halberg continued to shock me with these words:

– I know that you have submitted a chronobiological paper to an international scientific Journal. I read your paper. Let me say that I am very surprise to see that you are able to perform chronobiological investigations. How did you learn to use the *Cosinor Method*?

My reply was:

– I am in touch with Prof. Brunetto Tarquini and Prof. Salvatore Romano of Florence University, who helped me to perform the chronobiological analysis of my scientific data.

For those who don't know who were Prof. Tarquini and Prof. Romano, I must say that they have been respectively among the first Italian physicians and physicists, to be interested to Clinical Chronobiology, directly in connection with Professor Halberg (unfortunately, I must announce that Brunetto has prematurely passed away in 1998 at the age of only 60 years). I feel honoured to have had Brunetto not only as colleague but also as a scientist.

As a matter of fact, in 1990, under the leadership of Professor Tarquini, I and other Italian chronobiologists could realize in Italy the first Interuniversity Center of Clinical Chronobiology with laboratories at Firenze - Directive Center -; Bologna; Chieti "G. D'Annunzio"; Ferrara; Genova; L'Aquila; Modena; Napoli "Federico II"; Parma; Roma "La Sapienza", my University: http://www.uniroma1.it/strutture/centri/centrimiste/cronobiologia-clinica. (Regretfully, the day March 12, 2012 I could know that Prof. Salvatore Romano also passed prematurely away).

Returning to the history, Professor Halberg with conviction said:

– Why don't you come to Minnesota University in my Institute? It is a pleasure for me to invite you to attend the Chronobiology Labs as Visiting Professor from Rome University. Let me hope that you will accept this invitation.

Immediately I replied:

– It is a dream for me to come to your famous Labs for learning by you more and more on Medical Chronobiology. I am totally available to approach your Institute.

Professor Halberg told me:

– OK. I am going by car to Milan for flying back to my country. There, you could take the train for Rome. Please, be so kind to follow me so that we can arrange your visit to Minnesota University.

During the time spent travelling to Milan by car, Franz Halberg initiated to plan my scientific journey and sojourn in USA, proposing me to bring all the scientific data from my investigations in Chronobiology.

Visiting Professor at the Chronobiology Laboratories of Minnesota University in Minneapolis, USA

In August 1980 I was ready to leave Italy for going to the Chronobiology Labs at the University of Minnesota, 5-187 Lyon Laboratories, 420 Washington Ave. S.E, Minneapolis, MN 55455, USA. (Figure 1).

The first day I was there, Franz Halberg (Franz from now ahead) introduced me Professor Germaine Cornelissen (Germaine from now ahead), the Vice Director and Coordinator, International Womb-to-Tomb Chronome Initiative, and Doctor Robert B. Sothern (Bob from now ahead), the responsible for the computer section at the Labs.

Soon after the presentation, Bob asked me to analyze the scientific data of my chronobiological research. In a short time, via his Unix Operated PDP 11 minicomputer, he elaborated the chronobiological analysis along with the chronobiometric tests, the drawings and tables.

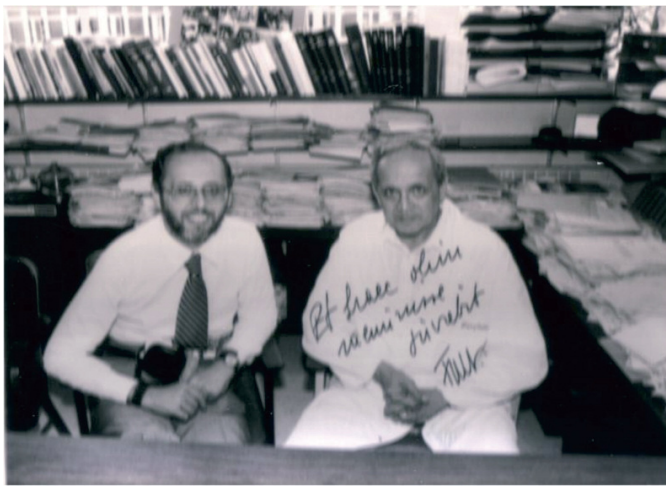

Figure 1. Prof. Franz Halberg (right) and myself (left) at the Chronobiology Laboratories of Minnesota University (USA) in 1980. The sentence written on the photo says: "Et haec olim meminisse juvabit", Franz.

Soon after, a person from the Documentation University Service came to the Labs, kept the iconography and in about one hour returned with the slides (the best at that time, those with the blue background) of all my scientific material.

At this time, Germaine taught me to retrieve the bibliography by telematically connecting the personal computer, assigned to me in a given room, to the National Library of San Diego, via the local University Library. In a short time, via the printer on my desk, I received the print out of the asked references.

After the completion of all these preliminary steps, Franz told me that the day after, at 01:00 p.m, I should held a Lecture on my investigation at the "Aula Magna", at the presence of the Dean as well as of the Academic Members of the Faculty of Medicine.

Believe me, what happened in these first hours of my presence at the Halberg's Labs was amazing and incredible. Please, consider that we were in 1980 and all the University Campus was already computerized and cabled. There was already the Internet, E-mail and the Gopher FTP on the Web.

With all the necessary material in my hands, I remained at the Labs all over the night for preparing the presentation. While going by feet to the Main Conference Hall, accompanied by Franz, Germaine and Bob, I had the surprise to see that all the other Institutes on Washington Avenue (the main street of the University Campus) were exposing, on their noticeboards, a poster, where it was announced my conference on the circadian rhythmicity of renin-angiotensin-aldosterone system (RAAS) in hypertensive states.

The Conference Hall was crowded by about 500 attendants of several racial and ethnic origins, belonging, as Professors, Physicians, Philosophical Doctors, Researchers, Lecturers, Visitors, Students at the Faculty of Medicine of Minnesota University.

I was presented to the Dean who, in his opening speech, introduced me to the audience. Thereafter, he asked Franz to make a preamble on the scientific research I was doing in Chronobiology. In deed, I was invited to reach the podium where I had the chance to speak for about 90 minutes to an ensemble that was very interested to my investigations because of the scanty knowledge on this topic at that time (my papers on the RAAS circadian rhythmicity are regarded as classics).

I was not aware the in American Universities, the attendants, including students, to a scientific conference can interrupt the orator for posing questions. So I had to answer to many interlocutors, who approached me with their own English pronunciation.

At the end of my presentation lasted one hour and a half, the Dean congratulated me for the interesting lecture and told Franz that my investigations were a further demonstration of the importance of Chronobiology in clinical medicine. Franz was very satisfied, me too.

Going back to the Labs, Franz confessed to me that I indirectly underwent a psycho-aptitude test for understanding whether or not I had the scientific preparation and personality for competing, at the level of an American University, with a cosmopolitan scientific community. I passed the test.

After this positive judgment, I was asked to cooperate in the Research Project: "From Womb-to-Tomb Chronome Initiative", dedicated to establish the international reference limits of 24-h blood pressure (BP) from neonates to centenarians. I was asked to provide a "large sample size" of clinically healthy Italian subjects in neonatal age as well in the latest decennials of life.

I was the first person of the Italian subjects to be investigated at the Chronobiology Labs.

With my surprise, I could see that they had already available some noninvasive automated devices for executing the ambulatory blood pressure monitoring (ABPM), that were coming from the experience of telematic spatial transmission of BP values of astronauts belonging to the NASA Programm Apollo. The first attempt of telemedicine all over the world.

At the Minnesota University, I had the chance to learn the in vogue informatic languages (Basic, Fortran, Pascal) as well as the most important methods of medical statistics, obviously including the chronobiological methods. This expertise allowed me to elaborate some new innovative methods of chronobiometric analysis, such as Cosint method [5] and Clinospectrometric analysis [6].

Figure 2. Visiting Professor at the Halberg's Chronobiology Labs. University of Minnesota (USA), in 1985 (left) and 1989 (right).

Figure 3. 1992, University of Rome "La Sapienza" of Rome, Italy. I am presenting to the audience Prof. Halberg who will held a magisterial lecture on Chronobiology.

Coming back to Italy and going forth to USA

Come back to my Institute of II Medical Clinic at the Policlinic Umberto I of Rome, I provided the University of Rome "La Sapienza" with the first Laboratory of Clinical Chronobiology.

The Lab was equipped with the first personal computers suitable for scientific research (informatic, telematic, telemetric applications), available in the '80s here in Italy, as well as with the ABPM devices, officially donated to the University "La Sapienza" of Rome by the "International Womb-to-Tomb Chronome Initiative" for letting me to cooperate to the construction of 24-h BP reference limits via a sample of clinically healthy Italians.

Gradually, via the research funds of MIUR (Ministero della Istruzione Universitaria) and CNR (Consiglio Nazionale delle Ricerche), the Lab was equipped with an adequate software for chronobiometrical analysis, written personally by me. It was connected via modem (the first one was an "acoustic coupler") to the C.I.C.S. (Centro Interdipartimentale di Calcolo Scientifico) of Rome University. The two rooms of the Lab were interconnected with a Netware 2.0 LAN to constitute an Intranet. The Lab was organized with printers, utilities, word processors, slide processor as well as new pressurometers and so on.

Finally, the Lab was structured as the Interuniversitary Center of Clinical Chronobiology of Rome University "La Sapienza" (http://www.uniroma1.it/strutture/centri/centri-miste/cronobiologia-clinica), equipped with the new incoming calculators either IBM compatible or APPLE.

Myself was called to teach to the first Doctorate in Clinical Chronobiology, organized and directed by Prof. Tarquini at the Florence University.

The set up of the ABPM data-base was on going. I could monitor neonates at the first day of life, adolescents, adults as well old people, *i.e.*, the ultraseptuagenaries living in Campodimele, a village known for the longevity of its inhabitants.

Because of my bilateral cooperation, I returned, as Visiting Professor, to the Chronobiology Labs in Minnesota in 1985 and 1989 (Figure 2).

The Cugini's Clinical Chronobiology Lab of Rome University hosted the most important chronobiologists of the world. Prof. Halberg, in person, in 1992 honored, as Visiting Professor, the Lab. In that occasion, I asked him to held a magisterial lecture on Chronobiology, that, however, was not a *psycho-aptitude test* but a *due tribute* to his magnificent human and scientific personality (Figure 3).

THE SCIENTIFIC ASPECTS OF THIS HISTORY

As one of first researchers, here in Italy, to have at his own disposal ABPM devices, I could collect, since 1980, a consistent group of normotensive as well as of hypertensive subjects. The recruited normotensives were regarded as *true normotensives*, not only because of the normality of their ABPM but also of a negative genealogic familiarity for arterial hypertension as well as of the lack of cardiovascular risk factors responsible for target organ damage (TOD).

The collected ABPMs gave origin to several papers [7-19].

The discovery of monitoring prehypertension associated to initial signs of TOD

In 1997, in my clinical activity as Professor of Internal Medicine, at the University Hospital, Policlinico Umberto I in Rome (Italy), I had the chance to observe that there were some subjects who, at the *office sphygmomanometry* (OS), were regarded as *normotensives* while, at the ABPM, they resulted to have an "*odd hour hypertension*". These *false office normotensives* were immediately excluded from the sample of the true normotensives.

In addition and importantly, I had also the opportunity to encounter some subjects (in summary 25 cases, 16 M, 9 F, mean age: 46±16 years) who showed *initial signs of hypertensive retinopathy* (Stage I of Keith-Wagener-Barker classification) resulting, however, *normotensives* at the OS and lacking of *risk factors* for target organ damage (TOD).

How to explain this conflicting clinical situation?

Naturally, I immediately thought that they could have an "*odd hour hypertension*". Therefore, I asked them to undergo the ABPM.

With surprise, *their ABPM did not show BP values higher than the pertaining day-night upper reference limits*. Therefore, I could exclude that they had a *masked hypertension* as suspected.

Thus, from an *intriguing situation*, I was drawn into a *true enigma*.

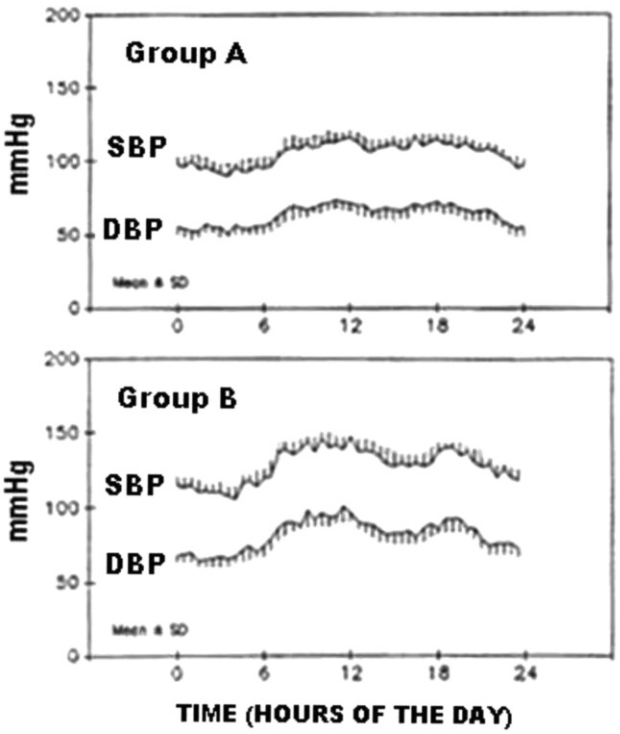

Figure 4. Mean chronograms of systolic (S) and diastolic (D) BP in true normotensives (Group A, left panel) and putative normotensives with initial signs of hypertensive retinopathy (Group B, right panel).

However, an explanation there should be, just for giving a clinical response to the main question of how to diagnose and treat these subjects.

An explanation could be a TOD of the retinal arterioles to a BP regimen not yet hypertensive. To confirm this hypothesis, I decided to statistically compare their BP regimen with that of the *true TODless normotensives*, considering the cases with retinal TOD as "*putative normotensives*".

With this idea in mind, I planned a retrospective study by randomly extracting, from my ABPM database, 25 *true normotensives*, matching for age and gender to the sample of the *putative normotensives* [20, 21].

I examined the ABPM of both the *true normotensives* (group A of controls) and *putative normotensives* (Group B to be compared), following these methodological criteria:

1. ascertain that there were no supranormal systolic (S) and diastolic (D) BP values all over the 24-h span as per a *masked hypertension*;
2. extract the Daily Mean Level of SBP and DBP within-day values [$DML_{(SBP/DBP)}$ in mmHg/24-h] for its statistical comparison between the Group A of true normotensives and the Group B of putative normotensives.

With a certain satisfaction, I could see by at a glance that the within-day SBP and DBP values in control Group A were visibly lower than those in experimental Group B (Figure 4).

Therefore, with an explainable anxiety I went to statistically compare the $DML_{(SBP/DBP)}$ of the two groups (Table 1).

As one can see from the second row, none of the subjects of the two groups showed intradiem SBP and DBP

Table 1. Number of supranormal intradiem systolic (SBP) and diastolic (DBP) blood pressure values as well as Daily Mean Levels of SBP and DBP along with the results of their statistical contrasts in investigated groups.

Selected parameters at the ABPM	Pressurometric variables	GROUP A True normotensives	GROUP B Putative normotensives with initial signs of hypertensive retinopathy	Statistical contrasts
				χ^2 test
Within-day values above 135/85 mmHg day-time), 125/75 mmHg (night-time)	SBP	0	0	NA
	DBP	0	0	NA
				t test (*p* value)
DML (mmHg/24-h)	SBP	112 ± 4	**123** ± 3	**<0.001**
	DBP	72 ± 2	**78** ± 2	**<0.01**

ABPM: Ambulatory Blood Pressure Monitoring; **DML: Daily Mean Level** given as Mean and Standard Error of the Mean; **SBP**: Systolic Blood Pressure; **DBP**: Diastolic Blood Pressure; ± **SEM**; **NA**: Not applicable

values higher than normal. By contrast, from the third row, one can see that the *putative normotensives* with a minimal hypertensive retinopathy showed the $DML_{(SBP/DBP)}$ to be significantly more elevated than that of the *true normotensives* (11 mmHg/24-h for SBP and 6 mmHg/24-h, p<0.001 and p<0.01).

Now, I could better explain the hemodynamic meaning of this tensive difference, according to the concept of Daily Baric Impact [12].

I invite you to consider that per each heart beat there is a pressure hit. This means that there is a numerical equivalence between the heart rate (HR) in beats per minute (bpm) and pressure rate in pulse per minute (ppm). Therefore, if we consider the HR DML and the BP DML, as estimated on the ABPM, it will be possible to calculate the SBP and DBP Daily Baric Impact (DBI) in mmHg/24-h as the product of the HR DMLxSBP or DBP DML, multiplied by the 1,440 minutes of a day-night cycle. Well, if we consider that in both the above-investigated groups A and B, the ABPM returned an almost comparable HR DML of 70 bpm/24-h, we can estimate that the SBP and DBP DBI will be given by respectively multiplying in Group A: SBP-DBI= 70x112x1440=11.289.600 mmHg/24-h and DBP-DBI= 70x72x1440=7.257.600 mmHg/24-h, and in Group B: SBP-DBI= 70 x123X1440=12.398.400 mmHg/24 and DBP-DBI= 70x78x1440=7.862.400 mmHg/24-h.

From these estimates, it clearly emerges the dramatic difference in DBI between the two Groups. Therefore, we should realize that a simple difference of 11 mmHg of SBP or 6 mmHg of DBP, between the two groups, causes the *putative normotensives* to have, on average, a SBP and DBP baric overload (Hyperbaric Impact) of 1,108,800 mmHg and 604,800 mmHg, respectively.

Ecce ratio!

The initial signs of hypertensive retinopathy could be explained by such an increase of the ***Daily Baric Impact*** (*i.e.*, a ***Daily Baric Hyperimpact***), on the retinal arterioles of the *putative* normotensives as compared to the *true normotensives*.

Due to the fact that nobody of the two groups was a masked hypertensive, I drew the logical inference that the *putative normotensives were showing an incipient retinal TOD* because of a BP regimen in between *true monitoring normotension* and *true monitoring hypertension*. I called this intermediate tensive regimen "Prehypertension" *alias* "Monitoring prehypertension" *alias* "ABPM-diagnosable-prehypertension" *alias* "Masked prehypertension".

Because of the association between the minimal reti-

Selected parameters at the ABPM	Pressurometric variables	GROUP A True normotensives	GROUP B Putative normotensives with initial signs of interventricular septum hypertrophy	Statistical contrasts
Within-day values above 135/85 mmHg day-time), 125/75 mmHg (night-time)	SBP	0	0	χ^2 test NA
	DBP	0	0	NA
DML (mmHg/24-h)	SBP	116 ± 2	**121** ± 2	*t* test (*p* value) <0.05
	DBP	69± 2	**72** ± 2	<0.05

Selected parameters at the ABPM	Pressurometric variables	GROUP A True normotensives	GROUP B Putative normotensives with initial signs of interventricular septum hypertrophy of the novel transplanted heart	Statistical contrasts
Within-day values above 135/85 mmHg day-time), 125/75 mmHg (night-time)	SBP	0	0	χ^2 test NA
	DBP	0	0	NA
DML (mmHg/24-h)	SBP	117± 2	**123** ± 3	*t* test (*p* value) <0.05
	DBP	72 ± 2	**81** ± 2	<0.05

Selected parameters at the ABPM	Pressurometric variables	GROUP A True normotensives	GROUP B Putative normotensives with initial signs of altered gestational blood flow of uterine arteries	Statistical contrasts
Within-day values above 135/85 mmHg day-time), 125/75 mmHg (night-time)	SBP	0	0	χ^2 test NA
	DBP	0	0	NA
DML (mmHg/24-h)	SBP	111± 3	**122** ± 3	*t* test (*p* value) <0.01
	DBP	71 ± 3	**78** ± 2	<0.05

Selected parameters at the ABPM	Pressurometric variables	GROUP A True normotensives	GROUP B Putative normotensives with initial signs of intrauterine growth retardation	Statistical contrasts
Within-day values above 135/85 mmHg day-time), 125/75 mmHg (night-time)	SBP	0	0	χ^2 test NA
	DBP	0	0	NA
DML (mmHg/24-h)	SBP	114± 2	**123** ± 2	*t* test (*p* value) <0.01
	DBP	73 ± 2	**80** ± 2	<0.01

Selected parameters at the ABPM	Pressurometric variables	GROUP A True normotensives	GROUP B Putative normotensives with initial signs of endothelial dysfunction	Statistical contrasts
Within-day values above 135/85 mmHg day-time), 125/75 mmHg (night-time)	SBP	0	0	χ^2 test NA
	DBP	0	0	NA
DML (mmHg/24-h)	SBP	111± 4	**128** ± 4	*t* test (*p* value) <0.001
	DBP	69 ± 2	**81** ± 4	<0.01

ABPM: Ambulatory Blood Pressure Monitoring; **DML: Daily Mean Level** given as Mean and Standard Error of the Mean; **SBP**: Systolic Blood Pressure; **DBP**: Diastolic Blood Pressure; ± **SEM**; **NA**: Not applicable

Table 2. Number of supranormal intradiem systolic (SBP) and diastolic (DBP) blood pressure values as well as SBP and DBP Daily Mean Levels (DML), along with the results of their statistical contrasts in investigated groups.

nal TOD and the prehypertensive regimen, I was obliged to think to a syndromic picture that I called:

"Minimal-change hypertensive retinopathy and arterial pre-hypertension" [20, 21}.

The enlarged "Tensive target organ damage and monitoring prehypertension syndrome"

After the above-cited study, I felt the need to confirm that monitoring prehypertension could be associated to the **initial TODs of the other cardiovascular districts.**

Therefore, I initiated a systematic research of *office normotensives* who were showing one of the TODs that could be instrumentally documented at that time, by verifying if their ABPM was showing a monitoring prehypertension.

I have preformed investigations [22-26} in the *following tensive TODs* of *office normotensives*:

1. Initial hypertrophy of interventricular septum (Table 2, first panel).
2. Initial hypertrophy of interventricular septum of the novel transplanted heart (Table 2, second panel).
3. Initial gestational altered blood flow of uterine arteries (Table 2, third panel).
4. Initial gestational intrauterine growth retardation of foetus (Table 2, fourth panel).
5. Initial alteration of post-ischemic forearm test as per a functional dysfunction (Table 2, fifth panel).

As one can see, all the panels show analogous results:

1. absence of supranormal intradiem BP values in both the investigated groups;
2. statistically significantly increased Daily Mean Level of SBP and DBP in *putative normotensives* with *initial signs* of TOD as compared to *true normotensives.*

Accordingly, I could draw the following conclusions:

1. because of the absence of supranormal within-day BP values, neither the *true normotensives* nor the *putative normotensives* showing an initial sign of TOD, could be classified as *masked hypertensives*;
2. because of the higher Daily Mean Level of SBP and DBP, all the *putative normotensives showing an initial sign of TOD* could be regarded as *monitoring prehypertensives*;
3. because of the systematic occurrence of a monitoring prehypertension, a tripartite classification of monitoring BP regimens seems to be mandatory (see ahead);
4. because of the non-occasional association of TODs with monitoring prehypertension, I could call the syndromic picture as the:

"Minimal tensive target organ damage/monitoring hypertension syndrome".

NATURAL HISTORY OF PREHYPERTENSION

Importantly, the papers describing the **"Minimal tensive target organ damage/monitoring hyperten-**

Table 3. Classification of high systolic (S) and diastolic (D) blood pressure (BP) for adults with reference to sphygmomanometric measurements.

JNC-6 (1997)		JNC-7 (2003)	
Stratification	**SBP/DBP (mmHg)**	**Stratification**	**SBP/DBP (mmHg)**
Optimal	**<120/80**	**Normal**	**<120/80**
Normal	**120-129/81-84**	**Prehypertension**	**120-139/80-89**
High-Normal	**130-139/85-89**		
Hypertension		**Hypertension**	
Stage 1 (mild)	**140-159/90-99**	Stage 1	**140-159/90-99**
Stage 2 (moderate)	**160-179/100-109**	Stage 2	**≥160/100**
Stage 3 (severe)	**≥180/110**		
Systolic (isolated)	**≥140/<90**	**Systolic (isolated)**	**≥140/<90**

JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Institutes of Health, Bethesda, Washington, USA

sion syndrome " have been consecutively published from 1997 to 2002 (20-26), when there was in vogue the classification of high BP by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in its Sixth Report (JNC-6) published in November 1997 [27, 28].

As you can see from the left panel of Table 3, in JNC-6 classification there was no mention of the sphygmomanometric class, called "Prehypertension". *No mention of the ABPM-diagnosable prehypertension*.

The diction "prehypertension" made its appearance in the Seventh Report (JNC-7) published in December 2003, and more extensively, as a pamphlet, in August 2004 [29, 30] by the Joint National Committee (Table 3, right panel).

Importantly, the JNC-7 classification, still active in USA, was referring to office sphygmomanometry. *No mention of the monitoring prehypertension*.

It is interesting to remark that the term "Prehypertension" was firstly conied by Robinson and Brucer in 1939 [31]. These two Authors were statisticians who investigated the range of normal blood pressure in a statistical and clinical study of 11383 persons. They noted that persons, showing a sphygmomanometric SBP and DBP range between 120-139/80-89 mmHg, were prone to develop a manifest hypertension later in their live. This means that these Authors intended arterial prehypertension simply as a potential factor of risk and not an actual condition of disease.

It must be stressed that the JNC-7 adopted *tout court* the Robinson-Brucer's SBP and DBP ranges leaving to the "office prehypertension" the same meaning of a preclinical BP regimen of risk. *No mention of the monitoring prehypertension associated with TODs.*

For these reasons, some investigators, making a revision of the pertaining literature on BP regimens, recognized that the description of the ABPM-diagnosable prehypertension was made in 1997 (six years before the JNC-7) with the precise meaning of a BP regimen responsible of TODs.

Because of this paternity, they felt the exegetic need to patronimically appeal the "Initial TOD/monitoring prehypertension syndrome" with the nosographic eponym of "Cugini's syndrome" [32-34].

BLOOD PRESSURE REFERENCE LIMITS FOR DIAGNOSING MONITORING PREHYPERTENSION AND CUGINI'S SYNDROME

In order to classifyBP regimens via ABPM I asked myself to calculate the reference limits for an ABPM-mediated diagnosis of BP regimens.

In approaching this problem, I realized, for coherence with the monitoring prehypertension, that the ABPM classification of BP regimens should be performed no more according to the classical criterion of a binary distinction between normotension and hypertension. There was the need of introducing the ABPM-diagnosable prehypertension, in that a real hemodynamic stage per se responsible of TOD.

As already mentioned I had a very huge collection of ABPMs gathered not only in true normotensives [7-19] and true prehypertensives [20-26], but also in true essential hypertensives [35-43].

Therefore, I thought to do a meta-analysis of my collected ABPMs for deriving the ABPM classification of BP regimens.

The classification derived by the meta-analysis is represented in Table 4.

CONCLUSIONS

This article is a kind of inverse narrative medicine in that it is not the patient to narrate the stories of his/her disease but the physician to tell about the history of a

Table 4. The first tripartite classification of normotension, prehypertension and hypertension applicable at the ABPM, as derived from a personal monitoring database.

Monitoring Blood Presssure Regimen	Within-day 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 **Cugini's syndrome**	**None** >135/85 (day-time) and >125/75 (night-time) IDEM	121-130/81-85 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.**

clinical syndrome that received the eponymic appellative of "Cugini's syndrome". This anecdotal presentation, however, has the same goal of the narrative medicine, i.*e.*, the role of fortifying clinical practice to better known what is the "Initials signs of TOD/monitoring prehypertension" not only by medical doctors but also by hypertensive patients.

For a long time it has been believed that normotension and hypertension were mutually exclusive diagnostic conditions (tertium non datur). Because of this binary conviction, it is not rare to assist at the clinical practice to make implicit and syllogistic diagnoses for which a patient is diagnosed as normotensive because not hypertensive and vice versa.

Methodologically speaking, a binary distinction is feasible if there are no other intermediate conditions between the two opposite situations. For example, this is the case for the words "Tall" and "Short" referred to height. Due to the fact that in between there is the "normal" stature, one is not authorized to diagnose as hypostatural individual, a person who is not tall, and vice versa. Notwithstanding this obviousness, in the last decade of the past century, it was still customary to regard as binary the criterion for diagnostically differentiating between normotension and hypertension.

The first novelty provided by the ABPM investigations made by me between 1997 and 2002 [20-26] was the incontrovertible demonstration that the diagnostic procedure for distinguishing the hemodynamic states, tending to a higher BP regimen, must take into consideration a third intermediate condition, the "monitoring prehypertension" (tertium datur).

As a second novelty, I provided the tripartite classification of BP regimens by giving the reference limits for differential diagnosis between normotension, prehypertension and hypertension. All of this was done with reference to the ABPM, a diagnostic procedure that is much more reliable in identifying derangements in BP regimens because of its ability to investigate the SBP and DBP 24-h pattern.

As a third novelty, I provided evidence that the monitoring prehypertension is a BP regimen that acts per se as a cause of TODs. Therefore, I promoted the prehypertensive status from a risk factor to a pathogenetic factor.

As a final novelty, I recognized, in the association of monitoring prehypertension and incipient TODs, a clinical syndrome, namely "Initial signs of TOD/monitoring prehypertension syndrome". As you have seen such a clinical association has received the eponym of "Cugini's syndrome".

Let me say that I am proud of this taxonomic assignment, not only for my person but also for the scientific staff that has cooperated in my investigations (Please, refer to my papers, cited in the chapter References, for knowing their Nominatives and Institutions), as well for my Institute of Second Medical Clinic, and last but not least for my country, Italy.

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