Hypertension, Arterial Mechanics and Other Issues

RICARDO J. ESPER[MTSAC, FACC, FAHAE]

Received: 01/04/201
Accepted: 02/16/2011

Address for reprints:
Ricardo J. Esper, M.D.
Virrey Loreto 2111
(C1426DXM) Buenos Aires,
Argentina
E-mail:
ricardo.esper@fibertel.com.ar

SUMMARY

Hypertension alters arterial wall function. The application of knowledge of the principles of arterial mechanics allows making more adequate diagnoses with better indications about how to treat patients.
The development of large clinical and treatment trials produced the so-called evidence based medicine. These studies have represented a significant advance in the knowledge of the natural history of diseases and allowed establishing the best therapeutic options. However, the patient seeking medical advice has personal, geographical, cultural and emotional conditions that, in most cases, differ from those of the patients selected in the trials, and require a variant of the therapeutic approaches used in those trials.
Treatment guidelines were designed on the basis of the results of evidence based medicine and are useful to reduce mistakes made by those who are not experts in the topic. The specialist should consider the particular patient he/she is facing using the knowledge provided not only by evidence based medicine but also by his/her personal experience and other ways of evaluation. In this way, the specialist can justify why he/she does not follow the recommendations suggested by the guidelines for his/her patient's benefit. Briefly, this would mean moving from only evidence-based medicine to personalized evidence-based medicine.

Rev Argent Cardiol 2011;79:371-376.

Key words > Hypertension - Arterial mechanics - Central pressure

Abbreviations >

HBP:	High blood pressure	**BP:**	Blood pressure

Pressure is a force exerted over a surface, but when this unit of force is exerted over a certain area, it is called stress. Using the example of arterial circulation, the force is exerted longitudinally to push the bloodstream (compressive stress) and transversely in 360º on all surfaces of the vessel circumference (tensile stress). Therefore, there are different types of pressure: longitudinal, transverse, circumferential or radial, and different interdependencies among them.

SOME ARTERIAL WALL PROPERTIES

The application of a force over a compliant material produces a deformation or an elongation of such material, called strain in the English literature. (1) The elasticity of biological tissues is reduced as pressure increases; for that reason, the response is not linear and, at some point, stress can cause damage in the tissues and even deform or break them. The application of a force over the arterial wall makes it elongate (strain). Once the force ceases, the wall returns to its prior state, a property that is called elasticity.

Any disease affecting the arterial tree disrupts its mechanics, and it leads to the impairment of its functions and of blood pressure (BP) levels. For example, atherosclerosis causes stiffness in vascular walls, leading to augmentation of BP, and conversely, augmentation of BP leads to greater stiffness in vascular walls. Greater arterial stiffness increases the speed of transmission of antegrade (or percussion) and retrograde (or reflexion) pressure waves. (2)

An easy way to explain what stiffness is would be to say it is like the decrease in compliance, but it is a simplistic definition which does not cover the whole situation. The consequences of stress variability, response to deformation, anisotropy, and non-linear viscoelasticity involve a complexity of very difficult consideration in a joint unique formula. The longitudinal pressure wave is simply a vibration of the wall caused by the cardiac activity. As the speed of this wave is inversely related to the compliance of the vessel, its increase is proportional to the arterial stiffness, and it is used as indirect parameter of vascular stiffness.

PRACTICAL RELEVANCE

During the first third of systole, heart contraction increases BP from diastolic to systolic values, generating a forward or percussion wave traveling

MTSAC Full Member of the Argentine Society of Cardiology
FACC Fellow of the American College of Cardiology
FAHA Fellow of the American Heart Association

at a velocity of 7-9 m/sec. At that same time, it ejects more than two thirds of its content in the vascular bed, which is carried through the great vessels at an average velocity of 1-1.20 m/sec. The arterial pulse changes as it travels from the central aorta down to the peripheral arteries; amplification of blood pressure from the aorta to the periphery occurs as a result of an increase in systolic pressure in the areas of higher resistance –bifurcation of the great vessels, particularly the iliac arteries– and the reflection of the cardiac pressure impulse at the level of the peripheral vessels (impedance) shapes the pulse waveform (Figure 1). (4) If peripheral vascular stiffness occurs, the reflection waveform is steeper and faster at the final third of the systolic pulse wave, resulting in increased augmentation of systolic and pulse pressures due to reflection, as observed in the elderly (Figure 2).

Conversely, in young individuals, low peripheral resistance results in a slower wave that does not affect the morphology of the pulse wave (Figure 3).

Not only does systolic waveform expand longitudinally toward periphery but also in all directions, even in circumferential direction, stretching the great elastic vessels that absorb the systolic pulse pressure wave. In the diastole, prior stages are recovered by arterial elasticity, increasing diastolic BP, that is, forming a second diastolic pulse (Windkessel model). Since this model does not work in the elderly because their arteries are stiffer, systolic BP is exaggerated and diastolic BP decreases. Therefore, most elderly subjects have higher systolic and lower diastolic BP levels, that is, an augmented "pressure differential", a phenomenon that exacerbates in increased pressure due to emotions or stress, in addition to systolic BP caused by the increased velocity of the pulse waveform. (3)

Tissue perfusion is performed by the BP that is absorbed at the precapillary level; for practical purposes, it is calculated as a third of the pulse pressure over diastolic pressure. The elderly absorbe peripheral pressures and the resulting mean BP ends up having equal or usually lower values than those of young individuals. This is of particular importance because lowering BP in an old individual means reducing perfusion pressure, which is immediately manifested in standing position, with low brain blood flow symptoms and consequences.

PULSE PRESSURE OR PRESSURE DIFFERENTIAL

The reflection wave over the percussion wave together cause augmentation of BP which does not show the reality, because it is different depending on the territory under consideration, and is different from aortic arch BP, as shown in Figure 4, with simultaneous pulse waves in different areas. That is one of the reasons that explains the different values of BP in clinical practice with commercial monitors that measure BP in the arm, the wrist or the fingers, and the reason why it is different from the BP measured in the aortic arch.

The pulse wave velocity is different depending on the territory evaluated. The wave velocity reflected in the bifurcation of femoral arteries is not the same as the slower velocity in the peripheral bed of legs or feet.

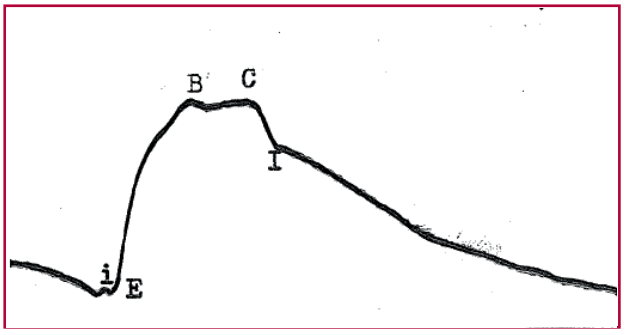

Fig. 1. Recording of external carotid pulse. The small **I** wave occassionally occurs during isovolumetric systole due to aortic sigmoid bulge to periphery. The **E** wave marks the beginning of carotid BP increase. The **B** wave is the percussion wave, and the **C** wave, the reflection wave. The **L** nadir is the aortic notch and indicates the beginning of diastole. Taken from Esper RJ & Madoery RJ. (3)

Fig. 2. Notice the telesystolic rise of the carotid pulse waveform –shown with the arrow–, for greater precocity and magnitude of the reflection waveform.

Fig. 3. Recording of the carotid pulse waveform in a young individual (**A**), in a middle-aged man (**B**), and in an elder individual (**C**). Taken from Esper RJ, Madoery RJ. (3)

Lower or upper limbs are not the same either. (5)

All these reasons explain the differences between aortic arch and brachial pressures in most of the population after the age of fifty, considered an

independent predictor of cardiovascular risk resulting from arterial stiffness. (6)

BLOOD PRESSURE ASSESSMENT

External BP measurement and pulse wave recording imply a series of devices that distort the real values. Pressure wave absorption or amplification caused by the tissues of a large arm is totally different from that of a thin arm, with little muscle mass. Readings even vary when different techniques are used, as is the case of oscilometric and auscultatory measurements.

Another factor to be considered is the great oscilation detected at the doctor's office, called "white coat pressure", and even omitting this effect. (7) In addition, a lot of time and long discussions and studies have been necessary to reach consensus on the usefulness and standarization of home BP measurement and outpatient pressure measurement. (8, 9)

Central BP measured on the aortic arch is a better predictor of cardiovascular events than brachial pressure, and it is a more reliable reference for calculating coronary diastolic filling. Jankowsky et al evaluated more than 400 patients in a mean follow-up of 4 years, and proved that major cardiovascular events increase 13% for each 10 mm Hg augmentation in aortic arch pressure. (10) The same was found in end-stage renal disease. Studies such as Strong Heart Study, (11) REASON (Preterax in Regression of Arterial Stiffness in a controlled doble-blind study), (12) CAFE (Conduit Artery Functional Evaluation), (13) ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial), (14) and many others come to the conclusion that aortic arch BP is superior to brachial pressure as prognostic indicator, and more appropriate for patients' follow-up. (15)

All this information suggests that measuring central BP is superior to brachial pressure regarding more accurate diagnosis, therapeutic follow-up, and prediction of cardiovascular risk, mainly for men and women older than 50 years of age. It can be performed noninvasively with the use of tonometers, similar to those used to measure eye pressure, with no risk to patients, but there are still no defined values considered as normal with this technique.

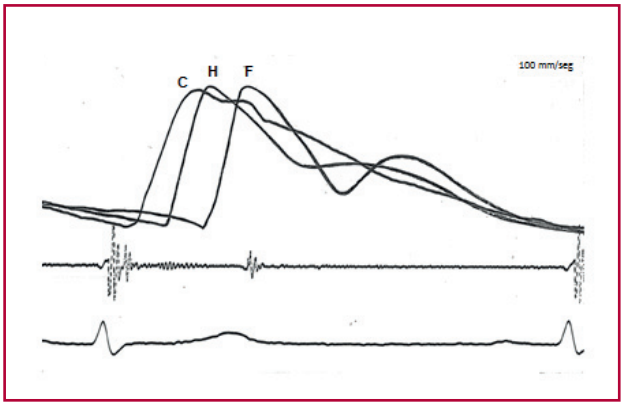

Fig. 2. External simultaneous recording of carotid (**C**), humeral (**H**), and femoral (**F**) pulse waveforms. Notice the delay of the foot of the humeral and femoral waveforms with respect to the carotid, which allow for calculation of pulse waveform; notice also the different waveforms due to the effects of peripheral beds and reflection waves. Taken from Esper RJ, Madoery RJ. (3)

COMMENTS

Major trials and treatment guidelines

At the beginning of the 19th century, Pierre Louis, a physician at La Charité Hospital in Paris, conducted a study of patients with pneumonia, in which he evaluated the impact of bloodletting by phlebotomy, which was a common medical practice at that time. He concluded that bloodletting was not beneficial but rather counterproductive; his study was considered as one of the initiators of evidence-based medicine. (16)

Nobody doubts the major benefits have been achieved with "evidence-based medicine", and the statistical methods to assess their outcomes. Major studies showed that hypertension (HBP) is a high risk condition with very high prevalence, whose incidence reduction has not been achieved yet. They have also demonstrated that some drugs are better than others, and that it is preferable to combine drugs than to increase the dose of one of them, but there are still huge doubts, particularly regarding the individual cases the physician faces in his/her office. (17)

HBP cannot be simply defined as the augmentation of BP values, and its treatment should not be limited to strict antihypertensive drug prescription in different doses. Also, progress does not proportionally depend on pressure levels, duration, or therapy time, and cannot predict the future of each individual case. The patient we face in our office is not always similar to that enrolled in large clinical trials, and has a completely different social, economic, geographical, cultural, personal, and emotional profile that forces the physician to use his knowledge to indicate the best treatment. Lately, this problem has attracked the attention, and the so-called narrative-based medicine, (18) or the "experience-based medicine" of the specialist have been suggested. (19)

The little research carried out in our country is funded by governmental agencies in the 70% of the cases, and the rest, by non-governmental organizations. But in the developed world, almost all research studies are funded by private sectors. (20) Major therapeutical trials have been conceived and designed under the medical regulations imposed in highly developed countries, especially in United States and Europe; but for financial reasons, those trials are carried out in developing countries, where not only medical practice but also social, economic, geographical, nutritional, and cultural conditions are usually different. Samples are performed in patients from the five continents for the purpose of homogenization; however, it only increases the differences. (21)

Major clinical studies have taught in some trials that coffee and its derivatives benefit cardiovascular diseases, but have stated that they are harmful in some others. They have also demonstrated that short sleep favors body weight increase, and at other times, that sleeping too much increases body weight.

Sometimes these studies punished carbohydrates as responsible for the epidemic of obesity, whereas other trials absolved them. Not to mention the aspirin, which was deified and then booted out. And we could go on discussing the antiatherogenic effects of alcohol, the beer effects on cancer reduction, and the list goes on. In principle, specialists are surprised at the comings and goings of results in trials, but finally they end up ignoring them. (22) The overall population moves between fear and acceptance of each finding according to their preferences, and end up by not trusting what their doctors indicate them. As Dr. Esther Díaz points out, "There is no pure science in search of knowledge for knowledge in itself", and she adds: "Behind each research study there is a market that finances the scientific advances, and which is not always impartial". (23)

On the other hand, guidelines for therapeutic processes are based on the outcomes of major clinical trials, that is, on the evidence. In addition, most members of the committees of design, follow-up, and assessment of major therapeutic studies and of these guidelines are professionals who are related with their sponsors. However, the guidelines are of great value for diagnosis and treatment of diseases, and they are even more useful when the operator is not well-trained, since they reduce the possibility of errors. Thus, they are assumed to provide a total return for paramedics, medical residents, and initiated physicians in the specialty; however, the specialist who is acquainted with pathophysiology and knows the problem in depth has the moral obligation to unfollow the guidelines when it is necessary and on a reasonable basis, using different treatments not included in them in order to provide the best therapy for each patient in particular. It is like resorting to a mixture of evidence-based, narrative-based, and experience-based medicine, and in many cases, finding new alternatives that solve the problem of each patient, which we could call occurrence-based medicine. (19)

Guidelines are a practical resource that reduce the effort of thinking and protect the professional physician from malpractice. In the medical environment, it is common to ridicule them with phrases like "the patient died, but the internal environment is in total equillibrium", as if the physician were satisfied by the mere fact of having followed the rules.

There seems to be no significant differences in therapies, clinical progress and prognosis between two patients with homocedasticity, one of them with a BP of 139/89 mm Hg and the other with 141/91 mm Hg, measured according to the guidelines of the JNC-7. The big difference is that the former is not eligible for therapeutic clinical trials, as opposed to the latter, who is eligible. Physicians who take part in clinical studies are under pressure by the inclusion of a certain number of patients in a predetermined period of time, and in order to fulfill this requirement they are not extremely selective in patient elegibility, especially when patients meet the inclusion criteria. In part, this might explain why the same drug in one trial is highly successful for HBP therapy –and it is even found to have positive effects over other antihypertensives–, (24) and in another trial the drug shows no benefits other than placebo. (25) It should also be important to consider how many of the patients included were only "white coat" hypertensives.

The Task Force of the European Society of Hypertension, based on the critical analysis of trials, concludes that there is no strong evidence in favor of recommending systolic blood pressure reduction to less than 130 mm Hg in high risk patients or in those who should receive antihypertensive treatment when blood pressure is within high normal limits. (26, 27) Other authors in the United States consider that prehypertension therapy (formerly called high normal) in primary prevention does not provide any benefit, and that only in secondary prevention some benefit can be obtained. (28)

Are all essential hypertensions equal?

To define what HBP is, the different opinions provided by many authorities on the subject end up being a detailed list of all the systems involved in its genesis and maintenance, with the increase in BP levels as common denominator. Perhaps the easiest and most accurate way to define it would be as a condition caused mainly by the increase of peripheral arterial resistance.

The problem is that the increase in BP causes greater peripheral resistance, and viceversa. Based on these arguments, it might be assumed that there would be two types of HBP that are confusing and considered to have the same etiology, progress and treatments. One of them, typical of young subjects, begins with an increase in peripheral resistance and mainly in diastolic pressure, and the other one, common among the elderly, is caused by the increased arterial stiffness and is mainly systolic; between both extremes, all the intermediate ranges are possible.

Therefore, it is the physician who must detect what patient he/she is dealing with, which evidence-based therapy is the best, what narrative is appropriate, what personal experience he/she has, and the special circumstances of the patient, in order to choose the best therapeutic option that ensures the lowest anxiety, the best adherence to treatment, the best quality of life, and the longest survival for the patient. It is a very difficult and not at all easy task to carry out, with the heath systems currently in use, which –mostly for economic reasons– are limited by the physician's time for consultation, the free choice of treatment, and, above all, by the discard of quality of the physician-patient relationship, so valuable in our medical, individual, and social culture.

CONCLUSIONS

Conclusion 1

Aortic arch BP by tonometry should start to be taken into account. While it does not modify the "white coat" BP, it is probably a more effective method to identify the impairments caused by arterial stiffness, although there is still no established consensus on normal values with this technique. (29)

Conclusion 2

Planning large clinical trials should not be resumed to the simple outcome of lowering blood pressure and evaluating hard –or not so hard– endpoints, almost always "tailored" to achieve certain outcomes.

Probably, it will be necessary to determine what type –mild, moderate, or severe– of hypertensive patients are to be assessed, what arterial stiffness level they have, and what –central or pheripheral– BP measurement should be considered, so as to sharpen the therapeutic approach and obtain outcomes more in accordance with clinical practice.

Conclusion 3

Should physicians put blood pressure monitoring in the hands of patients? Personally, I think it is inadequate. It may be a methodology that creates anxiety and concerns, which cause "white coat" hypertension and, in many cases, desperation, self-medication, or even unpredictable conditions.

As a result of this conclusion, prophylactic information for the population must be responsible, in order to detect a larger number of hypertensive patients and better adherence to treatment, but not to generate new pseudo-hypertensive patients.

Conclusion 4

The responsible parties should extend the time for medical consultation, provide physicians with time for study and research, as well as access to medical information. All these measures will reduce "white coat" hypertension and therapeutic excess or defects, allow for greater adherence to treatment, and achieve better quality of life and longer survival for patients. But, above all, they will reduce the social and labor cost, and the time has come in which those responsible for population health understand it.

RESUMEN

Hipertensión arterial, mecánica arterial y otras lides

La hipertensión arterial incide sobre las paredes de las arterias alterando su funcionalidad. La aplicación del conocimiento de los principios de la mecánica arterial posibilita diagnósticos más adecuados con mejores indicaciones terapéuticas para los pacientes.

Los grandes ensayos clínicos y de indicaciones terapéuticas generaron la llamada medicina basada en la evidencia. Han significado un enorme avance en el conocimiento de la historia natural de las enfermedades y permitieron establecer las mejores opciones terapéuticas, pero el paciente que se presenta ante el médico asistencial tiene condiciones personales, geográficas, sociales, culturales y emocionales que en la mayoría de los casos difieren de las de los seleccionados en los ensayos y requieren variantes dentro de los tratamientos resultantes de dichos estudios.

Las guías de indicaciones terapéuticas fueron diseñadas de acuerdo con los resultados de los estudios de medicina basada en la evidencia y son de gran utilidad para reducir los errores de quienes no son expertos en el tema. Pero el médico especializado debe considerar al paciente en particular que tiene frente a sí y utilizar los conocimientos que le brindaron no sólo la medicina basada en la evidencia, sino añadir el que surge de su experiencia personal y de otras formas de evaluación para que, fundamentada su resolución, pueda salirse de las prácticas aconsejadas en las guías en bien de su paciente. Brevemente, implicaría virar de la medicina basada sólo en evidencia a la medicina personalizada basada en evidencia.

Palabras clave > Hipertensión - Mecánica arterial - Presión central

BIBLIOGRAPHY

1. Lee RT, Kamm RD. Vascular mechanics for the cardiologist. J Am Coll Cardiol 1994;23:1289-95.

2. Yoganathan AP, Cape EG, Sung HW, Williams FP, Jimoh A. Review of hydrodynamic principles for the cardiologist: applications to the study of blood flow and jets by imaging techniques. J Am Coll Cardiol 1988;12:1344-53.

3. Esper RJ, Madoery RJ. Progresos en auscultación y fonomecanocardiografía. Buenos Aires: López libreros editores; 1974. p. 44-56.

4. Forcada P. Interpretación de los modelos de mecánica arterial: conducta elástica pasiva, activa y dinámica, y ecuación constitutiva de la pared arterial. En: Esper RJ, Kotliar C, Barontini M, Forcada P, editores. Tratado de mecánica vascular e hipertensión arterial. Buenos Aires: Intermédica; 2010. p. 91-100.

5. Brunner-La Rocca HP. Towards applicability of measures of arterial stiffness in clinical routine. Eur Heart J 2010;31:2320-2.

6. Reference Values for Arterial Stiffness' Collaboration. Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'establishing normal and reference values'. Eur Heart J 2010;31:2338-50.

7. Burgen S, et al. Is there a difference between current clinical recommended measurement techniques? 20th Scientific Assembly of the American Academy of Family Physicians. Abstract RS 015.

8. Majul C. Normativas de la medición de la presión arterial. En: Esper RJ, Kotliar C, Barontini M, Forcada P, editores. Tratado de mecánica vascular e hipertensión arterial. Buenos Aires: Intermédica; 2010. p. 399-402.

9. Caruso G, Fernández D. Monitoreo ambulatorio y variabilidad de la presión arterial. En: Esper RJ, Kotliar C, Barontini M, Forcada P, editores. Tratado de mecánica vascular e hipertensión arterial. Buenos Aires: Intermédica; 2010. p. 403-7.

10. Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, et al; Aortic Blood Pressure and Survival Study Group. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. Hypertension 2008;51:848-55.

11. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension 2007;50:197-203.

12. Protogerou A, Blacher J, Stergiou GS, Achimastos A, Safar ME. Blood pressure response under chronic antihypertensive drug therapy: the role of aortic stiffness in the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) study. J Am Coll Cardiol 2009;53:445-51.

13. Williams B, Lacy PS, Thom SM, Cruickshank K, Stanton A, Collier D, et al; CAFE Investigators; Anglo-Scandinavian Cardiac Outcomes Trial Investigators; CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation 2006;113:1213-25.

14. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al; ASCOT Investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet 2005;366:895-906.

15. Safar ME. Arterial aging– hemodynamic changes and therapeutic options. Nat Rev Cardiol 2010;7:442-9.

16. Yusuf S, Díaz R. ¿Qué es la cardiología basada en la evidencia?. En: Esper RJ, Machado RA, editores. La investigación en medicina. Buenos Aires: La Prensa Médica Argentina; 2008. p. 105-18.
17. Tajer CD. Ensayos terapéuticos, significación estadística y relevancia clínica. Rev Argent Cardiol 2010;78:385-90.
18. Tajer CD. Haciendo posible el debate sobre la medicina basada en evidencias. Rev Argent Cardiol 2010;78:459-66.
19. Vila JF. En: Lylyk P, Vila JF, Ingino CA, editores. Ataque cerebrovascular. Buenos Aires, 2010.
20. Pearlstein S. Health care's dilemma: competition or collaboration? The Washington Post 2010, 24 de noviembre, A11.
21. Bartlet DL, Steele JB. Deadly medicine. Vanity fair 2011;(1):1-12 http://www.vanity fair.com/politics/feature/2011/01/deadly-medicine-201101?printable=true
22. Himilian E. La ciencia contradice a la ciencia, un aporte a la confusión general. Los hallazgos pueden generar dudas en la gente. La Nación (Buenos Aires), 2010; 4 de diciembre: p. 1 y 32.
23. Díaz E. Las grietas del control. Buenos Aires: Editorial Biblos; 2010.
24. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.
25. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators, Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomized controlled trial. Lancet 2008;372:1174-83.
26. Mancia G, Laurent S, Agabiti-Rosei E, Ambrosioni E, Burnier M, Caulfield MJ, et al; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009;27:2121-58.
27. Zanchetti A. Blood pressure targets of antihypertensive treatment: up and down the J-shaped curve. Eur Heart J 2010;31:2837-40.
28. Oparil S. Hypertensive treatment. Vascular Biology Working Group Simposium, New Orleans, Abril 2, 2011.
29. Pepine CJ. Central BP measurement: Is clinical practice implementation near? Vascular Biology Working Group. Data Alert. 2010.