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REVIEW ARTICLE

From Riva-Rocci until Miocardial Intersticial Fibrosis: The Seven Errors Game in Arterial Hypertension - Misconceptions Review

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ABSTRACT

Knowledge of cardiac, renal and vascular injuries that occur in Arterial Hypertension has been known for a long time, however, their correlation with high blood pressure levels can only occur after the dissemination of the measure developed by Riva-Rocci and perfected by Korotkoff at the beginning of the 20th century. This correlation was initially imagined with false assumptions, which led not only to inertia but also to an opposition to the decrease in blood pressure levels that lasted around five decades. These false assumptions are named and analyzed. Even after the definition that the drop in blood pressure levels should be an obligatory part of the treatment of this condition, other erroneous understandings of this pathology have continued to occur until today. In this review, which covers the last one hundred and thirty years, we found, enumerated and analyzed seven of these errors based on the current knowledge we have gained on Arterial Hypertension and exposed their differences, simulating a game of seven errors.

The aim of Science is not to open a door to endless wisdom, but to put a limit on endless error.

Bertold Brecht: The Life of Galileo

Introduction

With this phrase by Bertold Brecht preceding his 1997 text on "Evolution of Hypertension Treatment from the 1940s to JNCV", Marvin Moser introduces this topic by stating that: "There are few stories in the history of Medicine that are filled with more errors or misconceptions than the story of hypertension and its treatment"[1]. This same author returns to the topic a decade later in "Historical Perspectives on the management of Hypertension"[2], now covering the period between 1950 and 2006. In Science, it is not uncommon for mistakes to precede successes, showing how much we can learn from them.

Even in a playful way, errors were part of our daily lives. When I was young, I had the habit of playing the game of seven errors, which consisted of observing two images and finding seven differences between them that we called errors. In this review, I want to use the seven errors, or better defined, temporary erroneous understandings that we found in the evolution of knowledge about Arterial Hypertension, increasing the time gap for the last 130 years, in addition to updating them.

The seven errors:

The first of them, in our opinion, occurred around 1895, when Scipione Riva-Rocci published his "new sphigmomanometro" in the Gazzetta Medica di Torino and at the same time the vasculopathy of arterial hypertension was described by Clifford Albutt with the German term *Essentielle Hypertonie* , translated into English as *Essential Hypertension*, which carried with it the concept that blood pressure levels were essential to be high to overcome the resistance of compromised arterioles and perfuse the tissues[3,4]. Therefore, lowering the pressure would have the effect of worsening tissue perfusion and therefore it would not be prudent to do so.

Although Nikolai Sergeyvih Korotkov described in 1905 that auscultation coupled to a sphygmomanometer could add information on diastolic levels and routine dissemination in the clinical practice of measuring blood pressure, its reduction was only advised in cases of Malignant Hypertension. In other words, 100 years ago there was the concept that after the age of 40, with each decade added to people's lives it was normal to add 10 mmHg and thus levels of 160 mmHg were normal for the 60 year old age group, 170 mmHg for the age group of 70 years and so on; we are facing the second of the seven errors (Figure).

This concept of high blood pressure levels as a defense that would prevent a decrease in tissue blood flow remained ingrained until the 1960s[5,6]. Proof of this is the publication in 1956, by George A Perera in the American Heart Journal, of the complications of 500 untreated hypertensive patients and their average survival in years after the involvement of target organ lesions at the cardiac level (4-8 years), renal (1-5 years) and cerebral (1-4 years)[7,8]. At the time, the understanding was that Arterial Hypertension, which would reduce survival by around 15 to 20 years compared to normotensive patients, had an uncomplicated and asymptomatic phase where educational guidance on the pathology was the only recommendation without therapeutic intervention and a complicated phase and symptomatic where the attempt to reduce blood pressure should be done with great care[8,9].

Figure shows German publication from 1936 differentiating "normal" levels in relation to age.

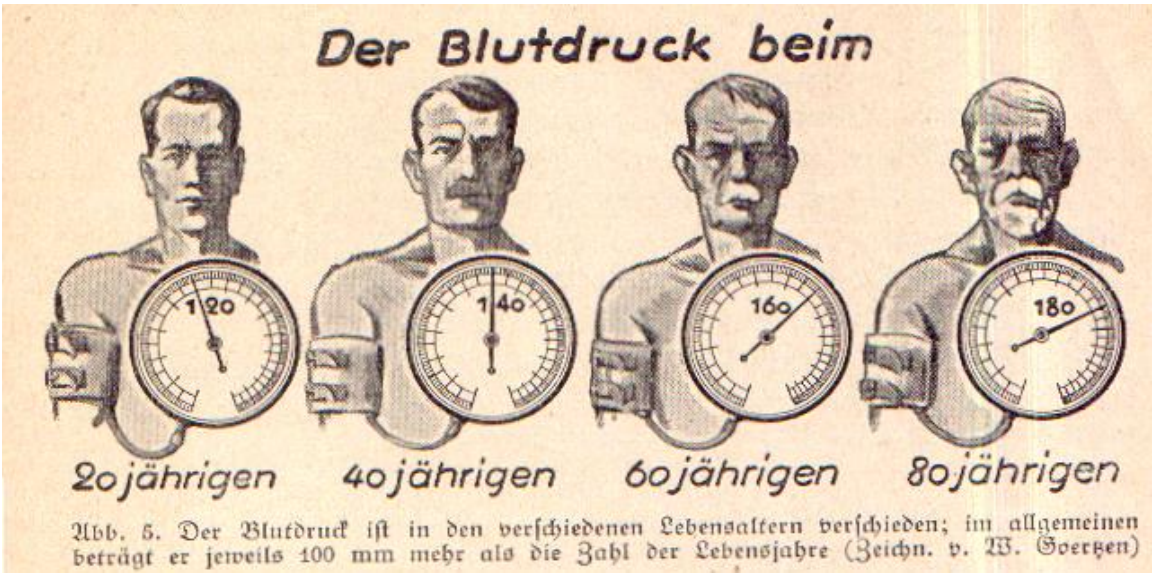
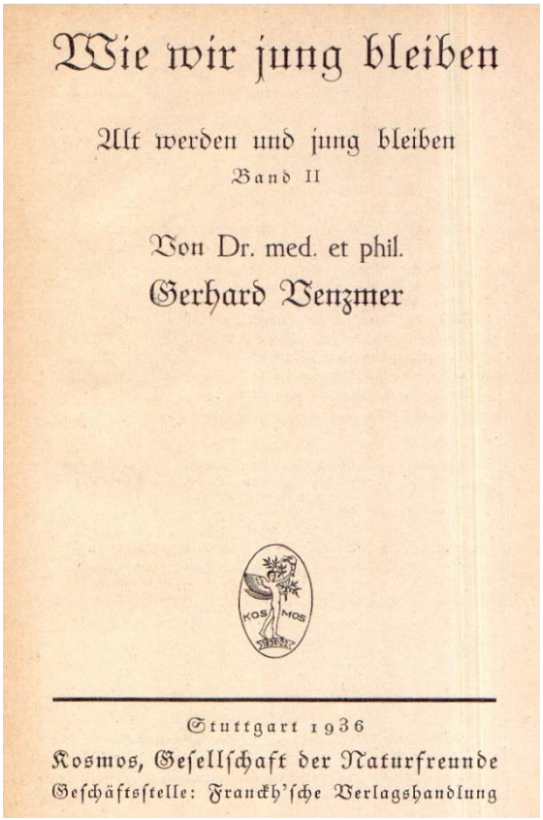


Abb. 5. Der Blutdruck ist in den verschiedenen Lebensaltern verschieden; im allgemeinen beträgt er jeweils 100 mm mehr als die Zahl der Lebensjahre (Zeichn. v. W. Goertzen)



At the end of the 1960s, the concept that high blood pressure levels are responsible for aggression and not a defense mechanism against compromised perfusion began to become robust. Those responsible for this paradigm shift were initially data obtained from the Framingham Heart Study, whose prospective follow-up had begun in 1948 [10] and from the Veterans Administration Study Group[11,12]. The question was "How much hypertensive disability justifies the treatment of hypertension?" becomes "How early must one start treatment in order to avoid or greatly reduce the occurrence of irreversible disabilities?"[13]

Evidence began to definitively show that the higher the blood pressure level, the greater the risk, independent of other variables, of being affected by cardiovascular complications such as heart failure, coronary events, strokes and renal functional damage and if associated with comorbidities such as diabetes, atherosclerosis, smoking and obesity this risk would be increased. With this information and still in memory of the loss of President Franklin D. Roosevelt due to cardiac and neurological complications of hypertension in 1945[2,5,14], task forces were proposed to guide the diagnosis and treatment of patients with this relevant pathology. This is how the Joints National Committee was born, the first being launched in 1977[1,15] and the second in 1980. In these two documents, diagnosis and therapeutic guidance were based only on diastolic blood pressure levels. Here we come across the third error, which was the disregard for systolic pressure levels for classification, risk assessment and therapeutic decision.

Over the years, after several JNC, Guidelines made by several Societies of Arterial Hypertension, Cardiology and Nephrology, in addition to documents from WHO Expert Committees, we noticed divergences in the normality values and therapeutic target that were adopted throughout the time. In our opinion, this was the fourth error, because what was Hypertension for some, was normotension for others, in addition to having different therapeutic goals, leading some hypertensive patients to think they were under control when in fact they were outside the safe goal we recommend nowadays. The fifth error is associated with the latter, because if the associated comorbidities increased cardiovascular risk, there was a delay in recognizing that in the presence of these, the therapeutic target should have different and lower levels than those of low-risk hypertensive patients[16].

The sixth error was revealed at the beginning of the 70s of the last century when the renin angiotensin aldosterone system was attributed the power to give the prognosis and also guide the most appropriate therapeutic choice if the renin dosage was low, normal or high. This was not confirmed by subsequent clinical evidence[17].

To introduce the seventh error, we first want to expose the belief that pharmacological interventions used in the treatment of hypertension, with emphasis on ACEI and ARB, are modifying the natural history and involvement of target organ damage. The classic involvement of the heart is left ventricular hypertrophy (LVH), let's discuss it in more detail. Initially, there was the perception that its genesis would result from a simplistic view that the heart would have its pump function overloaded by high peripheral resistance. Its presence would initially be seen by the LV overload seen on the ECG, or changes in the cardiac silhouette on the chest X-ray, learned from information coming from anatomical-clinical correlations. It was known that the cardiac involvement of hypertension was visually expressed macroscopically by the increase in the thickness of the LV walls and under microscopy by cardiomyocyte hypertrophy. With the introduction of echocardiography, it was possible to measure this thickness and increase the diagnostic sensitivity of cardiac target organ damage compared to ECG and chest radiography. Myocardial tissue is composed of myocytes, vessels, conduction system and scaffold containing fibroblasts and collagen. Echocardiographic measurement of the LV walls

would reveal the sum of all these constituents without differentiating them. However, we must remember that in cardiac target organ damage, the increase in these constituents (myocardium, framework and vessels) is not proportional. Thus, the predominance of the framework could lead to diastolic dysfunction due to changes in LV relaxation and inadequate neovascularization, compromising the coronary reserve. Today we know that LVH is caused by multiple triggers, with the autocrine and paracrine RAAS being the most important. Therefore, the pharmacological blockade of one of the main pathways that induce cardiac target organ damage (TOD). The RAAS may keep other triggers released or even enhance escape pathways, leading to the adaptation of the hypertensive patient to a new environment where the extracellular matrix would undergo changes that would culminate in myocardial interstitial fibrosis, namely: stimulus to the formation of type I and type III collagen, an increase in glycoproteins, glucosamino glycans and proteoglycans, as well as an increase in the production of growth factors and proteases. The end result would be predominantly reactive and non-reparative fibrosis[18,19]. There is already evidence of an association between myocardial interstitial fibrosis and risk factors for CAD such as Lp(a), which would increase the risk of ischemic outcomes in these hypertensive patients[20]. Excellent reviews of this topic have recently been published[21,22,23,24,25]. The analysis of this knowledge leads to new questions, for example, whether temporally the changes that occur in the framework, in the cardiomyocyte and in the vessels would be simultaneous in time and evolving at the same speed or would there be differences, would these be important in clinical practice? If Myocardial Interstitial Fibrosis temporally precedes other changes, it may perhaps explain the presence of ECG with fragmented QRS preceding the appearance of Arterial Hypertension in this small sample by Bekar et al[26] and the late ventricular potentials seen on high-resolution ECG only in patients with LVH resulting from Arterial Hypertension. with the presence of SVT and NSVT on Holter[27]. Both findings reflect heterogeneous conduction due to Myocardial Interstitial Fibrosis in our opinion. We have talked so far about the induction and progression of LVH, but the same reasoning applies to the regression of LVH that pharmacological treatment can induce; If regression does not occur simultaneously in the three compartments mentioned, we may obtain unfavorable outcomes with regression. We can still remember a hypertensive patient with concentric LVH with septum and posterior wall measurements of 24 mm, who after 6 months of aggressive treatment with various hypotensives drugs used not only for controlling blood pressure but also for regression of LVH, which was achieved with the new septum and posterior wall measurements of 18 mm but after that the patient developed atrial fibrillation and HFpEF. We were probably unsuccessful in the regression of myocardial interstitial fibrosis and worsened diastolic function and the aforementioned unfavorable outcomes. Let's wait for new research to show us whether this point of view outlined above is correct.

Conclusions:

The initial erroneous concept that high blood pressure levels were essential for maintaining perfusion led to inertia and resistance on the part of doctors at the time to take any therapeutic action that would result in lowering

blood pressure levels. This paradigm took half a century to be partially broken. The next question to be answered was in which patient and how much blood pressure levels should be reduced, while simultaneously we begin to have effective and safe pharmacological resources for the treatment of high blood pressure[5]. The next step was to discover that high blood pressure was not an isolated risk factor but rather a comorbidity associated with other metabolic disorders and that if cardiac, renal or vascular damage was evident, the therapeutic target would be to obtain lower blood pressure levels. Finally, nowadays, scientific evidence provides us with new knowledge about the pathophysiology of target organ damage at the cellular and molecular level[18,19,20,21,22,23,24,25].

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References:

1- Moser, M. Evolution of the treatment of Hypertension from the 1940s to JNC V. Amer J Hypertension 10:2S-8S 1997

2- Moser, M. Historical perspectives on the management of Hypertension. J Clin Hypertension 8(8) S2:15-20 2006

3- Allbutt, D. Senile plethora or high arterial pressure in elderly persons. Trans Hunter Soc,1895

4- Sambhi, M.P. Essential Hypertension In: Arterial Hypertension, J. Rosenthal (ed) Springer-Verlag New York, Inc. 1982

5- Rosenthal, T. Contemplating the history of Drug therapy for Hypertension. Blood Pressure 13:262-271 2004

6- Johnson, RJ; Feig, DI; Nakagawa, T; Sanchez-Lozada, G and Rodriguez-Iturbe, B. Pathogenesis of essential Hypertension: historical paradigms and modern insights. J Hypertens 26(3): 381-391 2008 doi:101097/HJH.0b013e3282f29876

7- Perera, G.A. Hypertensive vascular disease; description and natural history. J Chronic Dis. 1(1): 33-42 1955 doi:10.1016/0021-9681(55)90019-

8- Perera, G.A. The Lewis A Conner Memorial Lecture Primary Hypertension. Circulation XIII(3) 321-328 1956

9- Wertheim, R.; Deming, Q.B. Management of patient with primary (essential) hypertension. J Chronic Dis 1(5) 574-588 1955

10- Syed S. Mahmooda, Daniel Levyb,c, Ramachandran S. Vasanb,d, and Thomas J. Wang. The Framingham Heart Study and the epidemiology of cardiovascular disease: A historical perspective. Lancet 383(9921): 999–1008 2014. doi:10.1016/S0140-6736(13)61752-3.

11- Veterans Administration Cooperative Study Group on antihypertensive agents. Effects of treatment on morbidity in hypertension. Results in patients with diastokic blood pressures averaging 115 through 129 mmHg, JAMA 202:1028-1034 1967

12- Veterans Administration Cooperative Study Group on antihypertensive agents. III. Influence of age, diastolic pressure and prior cardiovascular disease; further analysis of side effects. Circulation. 45:991-2004 1972

13- Smirk, H. The prognosis of untreated and of treated hypertension and advantages of early treatment. Am Heart J 83(6) 825-840 1972

14- Wolf, M; Ewen, S; Mahfoud, F and Bohm, M. Hypertension: history and development of established and novel treatments, Clin Res Cardiol 107: S16-S29 2018 https://doi.org/10.1007/s00392-018-1299-y

15- Report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. JAMA. 237(3):255-61 1977

16- 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39, 3021–3104 2018 ESC/ESH GUIDELINES doi:10.1093/eurheartj/ehy339

17- Laragh, JH; Baer, L; Brunner, HR; Buhler, FR and Vaughan, JE. Renin, angiotensin and aldosterone system in pathogenesis and management of hypertensive vascular disease. Amer J Med 57(5) 633-652 1972

18- Harrison, DG; Coffman, TM and Wilcox, CS. Pathophysiology of Hypertension – The mosac theory and Beyond. Circulation Res 128: 847-863 2021 doi:10.1161/CIRCRESAHA.121.318082

19- Paulus, WJ and Zile, MR. From systemic inflamation to myocardial fibrosis. The heart

Failure with preserved ejection fraction paradigm revisited. Circulation Res128: 1451-1467 2021 doi:10.1161/CIRCRESAHA121.318159

20- Chehab, O; Abdollahi, A; Ehelton, SP; Wu, CO; Ambale-Venkatesh, B et al. Association of Lipoprotein(a) levels with myocardial fibrosis in the Multi-ethnic study of atherosclerosis. J Amer Coll Cardiol 82(24)2280-2291 2023

21- Frangogiannis, NG. Cardiac fibrosis. Cardiovasc Res 117: 1450-1488 2021 doi:10.1093/cvr/cvaa324

22- Gonzalez, A; Lopez, B; Ravassa, S; San Jose, G; Latasa,I et al. Myocardial interstitial fibrosis in hypertensive heart disease: from mechanisms to clinical management. Hypertension 2024 doi:10.1161/hypertensionAHA.123.21708

23- Nemtsova, V; Visher, AS and Burkard,T. Hypertensive heart disease: A narrative review series – Part 1: Pathophysiology and microstructural Changes. J Clin Med 12:2606 2023 https://doi.org/10.3390/jcm12072606

24- Nemtsova, V; Burkard, T and Visher, A. Hyertensive heart disease: A narrative review series – Part 2: Macrostructural and functional abnormalities. J Clin Med 12:5723 2023 https://doi.org/10.3390/jcm12175723

25- Nemtsova, V; Visher, AS and Burkard,T. Hypertensive heart disease: A narrative review series – Part 3: Vasculature, biomarkers and the matrix oh hypertensive heart disease. J Clin Med 13:505 2024 https://doi.org/10.3390/jcm13020505

26- Bekar, L; Katar,M; Yetim, M; Çelik, O; Kilci, H and Onalan, O. Fragmented QRS complexes are a marker of myocardial fibrosis en hypertensive heart disease. Turk Kardiyol Dem Ars 44(7) 554-560 2016 doi:10:5543/tkda.2016.55256

27- Pinho, C; Dias, DL; Figueiredo, MJO; Rocha, JC; Fornari, N et al. Correlation between ventricular arrhythmias and geometric remodeling of the left ventricle in essential hypertension. Arq Bras Cardiol 61(4) 1993