**REVIEW**

**Assessment of Arterial Stiffness in Patients with Resistant Hypertension:**

**Additional Insights into the Pathophysiology of this condition?**

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**Abstract**

Good understanding of the pathophysiological mechanism(s) ofresistant hypertension (RH)andthe relationship tovascular dysfunction is important for optimal blood pressure control.

The aim of this review article is to summarise the available data on the methods of arterial stiffness assessment, and their usefulness in RH. Several studies that provide information on the non-invasive methods of evaluation of arterial stiffness have been discussed; specifically, pulse wave velocity (PWV) and augmentation index (AIx) tests. Increased arterial stiffness, elevated AIx and impaired endothelial function all act as indicators and predictors of cardiovascular events in patients with hypertension.

Our review suggests that PWV and AIx are impaired in patients with severe hypertension. Early assessment of these characteristics can potentially be of value in patients with RH.

**Introduction**

Hypertension is a significant risk factor for cardio- and cerebrovascular diseases such as stroke and heart failure.1 In Europe, 30-45% of the general population suffers from hypertension (HTN) and it is expected that by the year of 2025 the prevalence of HTN will continue to rise by 15–20%.2

High blood pressure can be associated with autonomic dysfunction, vascular impairment and abnormal cardiac mechanics.3-5 Both endothelial impairment and increased arterial stiffness have been associated with HTN 6; however, the relationship(s) between high blood pressure and arterial stiffness are less clear. Increased arterial stiffness, elevated augmentation index and impaired endothelial function may all act as indicators and predictors of cardiovascular events in patients with HTN.

Although lifestyle modifications and drugs can be effective in most cases of HTN, blood pressure control is difficult to achive in a subgroup of patients. According to the European Society of Hypertension and the European Society of Cardiology (ESH/ESC) guidelines for the management of arterial HTN, up to 10 % of patients with HTN will develop so-called ‘resistant hypertension’.2 Resistant hypertension (RH) is diagnosed when office systolic and diastolic blood pressures exceeds 140 mmHg and 90mmHg respectively despite the use of three or more antihypertensive medications, one of which is a diuretic.2 RH is associated with a poor prognosis due to a higher risk of target organ damage (TOD) 7 and has an adverse effect on endothelial function, cardiac mechanics and autonomic function, as well as increased arterial stiffness.8,9

Understanding the pathophysiological mechanism(s) underlyingRHandits relationship tovascular dysfunction is an important factor to manage this condition and minimise complications. Effective management of HTN is of particular importance. Studies have shown that lowering systolic blood pressure by 10 mmHg reduce the risk of coronary artery disease (CAD) by 20%, stroke by 35%, heart failure by 40% and all-cause mortality by 10-15%.10-12

The aim of this review article is to summarise the available data on the arterial stiffness assessment methods, and their usefulness in RH. Several studies that provide information on the non-invasive methods of arterial stiffness assessment are discussed, specifically, pulse wave velocity (PWV) and augmentation index (Aix) tests. The ESH/ESC guidelines, recommend assessment of both endothelial and arterial stiffness alterations in the RH population2. Hence, the non-invasive evaluation of these parameters may provide insights into the pathophysiology and treatment of HTN.4

**Methods**

A comprehensive literature search of PubMed was performed using the following keywords: “arterial’’, “stiffness’’, “vascular’’, “Pulse’’, “wave’’, “velocity’’, “augmentation’’, “index’’, ‘’resistant’’, “hypertension’’. The relevant articles were selected following the screening of the titles and abstracts (Table 1).

**Basic Principles**

Arteries have thick walls to accommodate blood flow and its great pressure. The structure of the arterial wall consists of three different layers; intima, media and adventitia. The intima (inner layer) is composed of endothelial cells and connective tissue while the middle layer, which is known as tunica media, contains elastic tissue and a thick layer of smooth muscles. The outer layer, commonly known as adventitia, consists of fibrous connective tissue.13

One of the primary functions of arteries includes blood flow transit and supply of oxygen to the tissues (i.e. a conduit function). The other function is to dampen and smooth the flow pulsations (cushioning function) which can be compromised when the artery becomes stiffer.14,15 During systole, blood is ejected from the left ventricle through the aorta to the arterial system.14,15 As a result of blood flow movement within the aorta and then arteries, a pressure wave is generated and transmitted through the arteries. When a pressure wave arrives at arterial bifurcations, a reflected wave is generated, which interacts with the pressure wave producing the aortic pulse wave, and shaping the arterial pulse. The ventricular function and aortic elasticity have an effect on the transmitted wave. On the other hand, the reflected wave is influenced by a number of factors; the elasticity of the entire arterial circulation, PWV, and the reflection site distance from the heart. 14,15

The pathophysiological mechanism of arterial stiffness can be defined as the changes in the properties of the arterial wall.16,17 It plays an important role in blood pressure regulation and cardiovascular function.18 Arterial remodelling occurs as a result of complex modifications including structural, mechanical and functional alterations, which eventually lead to rigidity of the artery. Arterial stiffening is associated with expanding and recoiling of arterial wall per heartbeat, which has a relationship with nitric oxide (NO), endothelial and vascular smooth muscle cell (VSMC). The degree of stiffness occurs can be different from one artery to another according to the elastic properties of each artery.16 Indeed, elastic properties in the tunica media of each artery determine the ability of the artery to recoil back when the pressure returns to its relaxed status. Expanding of the aortic wall in systole is determined by two factors, systolic blood pressure (which is controlled by blood volume ejected in the systole) and the accumulating elastic energy of the vascular wall. The stored elastic energy acts in diastole phase to maintain continues perfusion and pressure in the aorta and arteries.13

As mentioned above, arterial stiffening is associated with alteration of VSMC and endothelial cells function. VSMC are affected and stimulated by several factors, which include mechanical cell stretching, fluctuations in calcium signalling, angiotensin II, endothelin, oxidative stress and NO.19-22 On the other hand, endothelial cell impairment produces an imbalance in the production and breakdown of vasodilator and vasoconstrictor substances, particularly in the production of NO and angiotensin II.23 NO is produced by endothelial cell and acts as a signalling molecule. Release of NO leads to VSMC relaxation and has a vasodilation effect to improve the blood flow. Impairment of NO production would contribute to oxidative stress and lead to impaired endothelium-dependent dilation which increases arterial stiffness.16

**Arterial stiffness Assessments**

Several methods are used to quantify arterial stiffness, including cardiovascular magnetic resonance (CMR), cardio ankle vascular index (CAVI), central blood pressure, pulse pressure, AIx, and PWV. Of the various methods proposed, carotid-femoral PWV (cfPWV) and AIx are widely considered as the least invasive, safest, and more reliable in terms of accuracy, as recommended by the ESH in 20182 and earlier by expert consensus document of 2006.24 PWV is estimated noninvasively by measuring the distance of arterial pulse between two superficial arterial sites (e.g. carotid artery and femoral artery) and the travel time taken.25 PWV is inversely correlated to arterial compliance, therefore in a stiff artery, the reflected waves arrive at the heart earlier due to high PWV and this leads to increased pressure and decreased flow in late systole. This causes an elevated central pulse pressure (PP), ventricular load, low ejection fraction, and high myocardial oxygen consumption.26

Furthermore, a scientific statement in2015 published by American Heart Association 16 recommended that measurement of arterial stiffness can help to predict cardiovascular events and it is an effective factor for risk stratification in relation to high blood pressure treatments.8,27 In addition, increased arterial stiffness may be an independent prognostic factor for the occurrence of cardiovascular events in patients with arterial HTN, such as coronary heart disease, congestive heart failure and stroke.28-31

The second recommended assessment of arterial stiffness is AIx. It is mathematically derived quantification which describes the association between the central blood pressure and the arterial pressure wave, including the forward and the reflected waves. The heart rate, travel time of the reflected wave, PWV, LV ejection, structure of the artery at reflection sites and certainly blood pressure level are factors that determine this index.32,33 AIx is estimated by calculating the following equation:

× 100

Where Ps: initial systolic pressure; Pi: pressure at inflection point; Pd: diastolic pressure;

(Ps – Pi) refers to the augmentation pressure; (Ps – Pd) refers to pulse pressure.34

**Arterial Stiffness and Resistant Hypertension**

HTN is the second most important risk factor of increased arterial stiffness after ageing.35 In 1808, Young et al 36, was one of the first to emphasis the association between blood pressure and what we now know as PWV. Recent studies 37-44 closely linked the presence of increased arterial stiffness and RH, assessed by PWV and AIx as shown in Table 1. Chung et al 37 evaluated 142 of RH patients aged above 65 years and showed that PWV was significantly associated with the incidence of RH (*P* = 0.015); however, this finding could be related to the presence of some comorbidities such as diabetes mellitus (DM) in RH group compared to the controlled group which can be behind the progression of arterial stiffness. Pabuccu et al38 showed the same possible linking of impaired AIx and PWV to resistant group, which were markedly elevated compared to the controlled group (*P* = 0.03 and *P* < 0.01). Faria et al 39 evaluated an RH group and showed significantly elevated oxidative stress determined by 8-isoprostane, suggesting some contribution of oxidative stress to endothelial dysfunction in resistant hypertensives. Nevertheless, this is a cross-sectional study and any causality cannot be concluded. Also, Barbaro et al 42,43 reported that when compared to healthy control groups, patients with RH had higher PWV in association with elevated elevated tumour necrosis factor-𝛼 (TNF-𝛼) levels in RH 42 and inflammatory cytokines.43

Conversely, a longitudinal study from the Framingham Heart Study41 demonstrated sustained arterial stiffening in both groups of hypertensives (controlled and uncontrolled treated) irrespective of the blood pressure level achieved at the end of the follow up. These findings give an important insights into the relationship between elevated PWV and residual cardiovascular disease (CVD) risk in patient with HTN, whether it is well controlled or resistant to treatment. However, the study group was defined as ‘uncontrolled hypertension’ which may be different than RH per se. Long standing duration of HTN is likely the reason of irreversible arterial changes despite better control of blood pressure.

Hemodynamically all above findings are linked to the fact that as HTN progressed and becomes sustained, there is some degree of vascular remodelling. In hypertensive patients, the main direct structural alteration of the arterial wall is hypertrophy of tunica media.45 Furthermore, systolic blood pressure is directly correlated to the degree of the aortic stiffness.13

HTN is a complex of alteration in several mechanisms that naturally regulate normal pressure.45 These mechanisms included, renin-angiotensin-aldosterone system (RAAS), renal system, and the sympathetic nervous system, all have an indirect effect on VSMS function and arterial remodelling. For example, high activation of RAAS has a significant effect on the progression of the increased stiffness in HTN population, because angiotensin II causes VSMC hypertrophy and collagen accumulation, while aldosterone activates growth of extracellular matrix by fibroblasts. Both changes have an adverse effect on functional properties of arteries.45 Genetic predisposition is another mechanism leading to stiff arteries in hypertensive individuals.46

Finally, as can be seen from Table 2 the majority of studies included patients who were diagnosed as RH, according to ESH/ESC guidelines or AHA statement with the exception of two studies 37,47. Only three studies assessed drug adherence 39,43,47 to confirm RH.

**Arterial Stiffness and Target Organ Damage**

The central blood pressure is the pressure reflecting the perfusion pressure of the heart, brain and kidney. Therefore, elevation of central BP has consequences that impact almost the entire body systems. Indeed, cfPWV measurement was an independent indicator of the degree of vascular damage48,49 and TOD in HTN.2,50 Worsening of arterial stiffness is also linked to the increased risk of stroke and kidney failure due to the damage of the brain and renal vessels.26 Increased arterial stiffness assessed by PWV has been shown to be an independent predictor of all-cause mortality in end-stage kidney disease51 and in HTN.28 In the HTN patient population with no history of CVD, increased PWV may act as an independent predictor of patients who are at high risk of cardiovascular events.52

A meta-analysis of 17 studies included 16,000 participants who were observed for 7.7 years53 showed that each 1 m/sec augmentation of PWV increase the rate of cardiovascular morbidity/mortality, and all-cause mortality by 15%. Moreover, Zuo et al concluded that with each 1 SD increase in central augmented pressure, the risk of cardiovascular events or death from CVD in the elderly rose by 1.4 fold.30

**Impact of Comorbidities and Age on Arterial Stiffness**

The progression of arterial stiffness exacerbated by the presence of comorbidities, and by ageing as demonstrated in Figure 1.Arterial stiffness and HTN share a number of risks, including chronic kidney disease (CKD), DM, obesity, female sex 44, black race and old age (Figure 2).50,54

***Age and acceleration of PWV***

As people age, arterial stiffness increases independently of blood pressure elevation.55,56 Lajemi et al 55 and Benetos et al 56 have linked older age to the progression of PWV in normal population and in controlled HTN population who are ≥50 years old. Both results are expected because age is the major contributing factor leading to the progression of arterial remodelling and PWV acceleration. Several mechanisms are implicated in this progression: elastin fragmentation, increased elastase activity, high collagen production by VSMC, elevated cross-linking of collage, altered growth factor regulation/tissue repair mechanisms, tunica media calcification, low NO production, high production of extracellular matrix of the media and adventitia and wider PP as a result of low compliance. All these factors make the arteries stiffer and less resilient, independent of BP elevation.45,47

***Impact of Hypertension and Diabetes Mellitus***

Concurrent of HTN and DM is highly prevalent, and the frequency of HTN rates is nearly twice in diabetics compared to the normal population.57 It is expected that the risk of CAD, stroke, nephropathy and retinopathy is higher in both HTN and DM population. The common mechanisms of association between those two conditions are involving elevated blood pressure, imbalance of the RAAS and vascular disorders.57

Tedesco et al 58 has examined the effect of concomitant DM and HTN on arterial stiffness changes, using PWV assessment. An elevated PWV was found among those who had HTN and DM compared to those who had DM or HTN alone, and when compared to control group with no HTN or diabetes. Elevated arterial stiffness in DM was associated with increased glucose levels, which augment the production of non-enzymatic glycation and high collagen accumulation which changes the mechanical characteristics of the arterial wall. Moreover, low insulin sensitivity is associated with a decline in vascular compliance.59 For these reasons, it is expected that combination of HTN and DM results in a degree of arterial stiffness that is markedly elevated, as opposed to the extent seen in HTN or DM alone.

***Impact of Hypertension and Kidney Disease***

Concomitant uncontrolled HTN and renal dysfunction are common, and HTN is considered one of the most significant causes of kidney impairment after DM.2 Arterial stiffness and vascular dysfunction increase progressively as kidney function deteriorates. Elevated proteinuria and high salt consumption are independently linked with both CKD and RH.60,61 At the same time, proteinuria and high salt consumption are closely associated with impaired endothelial function and increased arterial stiffness.61,62 In fact, proteinuria has a strong predictive value for the presence of vascular dysfunction in patients with CKD.63 Increased total body sodium may also lead to arterial stiffening, which is reflected by high PP with renal impairment.64 Vascular dysfunction in renal disease population is also associated with low glomerular filtration rate, as well as dilated vessel diameter with preserved wall thickness, resulting in increased wall stress.65,66 cfPWV is found to be high in CKD population compared to HTN and healthy subjects, indicating that the severity of the arterial stiffening progresses more in the CKD population.66-68

***Impact of Hypertension and Heart failure***

Elevated BP is common in patients with Heart Failure (HF) which contribute to a worse outcome.69 Development of arterial stiffness is closely linked with impaired systolic and diastolic LV function.70 The impact of elevated arterial stiffness on the risk of developing heart failure are not well-known. On the other hand, patients with HF have increased arterial stiffness with both preserved function (HFpF) 71 or reduced function (HFrF). 72

In the longitudinal Framingham Heart Study 73, 2539 participants without clinical HF were observed for 10 years and examined every 2 years. Central PP, AIx and cfPWV were evaluated. A total of 170 participants developed HF during the follow up, and HFpF occurred in (43%) and HFrF occurred in (34%), while in 23% of patients, the diagnosis was unclassified. High PWV was associated with an increasing risk of having HF of both subtypes.

One possible hemodynamic mechanism of HF development is that high arterial stiffness leads to increased LV and cardiac load.70 Also, the imbalance between myocardial oxygen supply and demand may occur due to LVH and reduced diastolic BP (frequently associated with abnormal arterial stiffness), resulting in low myocardial perfusion and subendocardial ischemia. 74 Furthermore, high arterial stiffness may lead to impairment of the intima by increase blood flow shear stress, thus contributing to atherogenesis.75

***Impact of Hypertension and Atrial Fibrillation***

HTN increases the risk to develop atrial fibrillation (AF), and increasing arterial stiffness is a contributing factor to incident AF 76-79. For example, the Framingham study 77 linked aortic stiffness PP to higher AF occurrence and recurrence rates. Each 10 mmHg increase in PP leads to the increase risk of developing AF by 12%. Lee et al 78 investigated the association between AF and arterial stiffness, using PWV assessment. The study demonstrated that presence of AF results in elevated arterial stiffness, independent of age or BP in the hypertensive population. All above findings can be explained by the following pathophysiological changes: aortic stiffness reflected by high PP may contribute to the increase cardiac load 80 causing ventricular hypertrophy 81 that results in ventricular diastolic dysfunction 82 and remodelling (dilated atrial and high atrial pressure).83 All these would lead to electrical changes in the atrium contributing to increase risk of developing AF.79

***Impact of Antihypertensive Drugs***

High blood pressure is associated with both high arterial stiffness and low compliance. Thus, in order to reduce systolic blood pressure, arterial stiffness and PWV need to be lowered. Therefore, several cardiovascular agents have different impacts on the structural and functional properties of the artery. However, the effects of antihypertensive medications on arterial stiffness can be direct or indirect. Many antihypertensive medications reduce arterial stiffening by lowering mean arterial pressure, reducing wave reflection and increasing the compliance. While others could cause further functional changes of arterial properties leading to arterial stiffness improvement.

Angiotensin-converting enzyme (ACE) inhibitors,84-86 β-blockers (BB) 87, diuretics (DIU) 88, calcium antagonists (CA), and angiotensin receptor blockers (ARB) 85,89 all showed therapeutic effect on arterial stiffness, to varying degrees, regardless of the effect on brachial BP. The reduction occurred either acutely or over a long period of follow up. Diuretics and β-blockers lower BP but have minimal impact than all the other antihypertensive agents in decreasing arterial stiffness.87

In addition, aldosterone blockers reduce cfPWV and Aix 90,91 by enhancing NO bioactivity and improving endothelial vasodilator function.92 Another small study showed spironolactone was efficient at lowering blood pressure and improving arterial stiffness in patients with HTN and DM.88

The ACE inhibitors 93, ARB, and CCB are the most widely used vasodilator agents and showed direct effect on arterial stiffness independent of blood pressure reduction.94 Herata et al 95, evaluated the effect of ramipril and atenolol in participants who have one or more coronary risk factors, and found that the ramipril group showed significant decline of the central pressure by 5.2 mmHg (Table 3). This finding seems to be consistent with other study 84, which showed an improvement of arterial stiffness after using ramipril in patients with peripheral artery disease (PAD), where there was an improved aortic compliance by (0.10 ±0.02 mL/mm Hg) and decreased PWV by (1.7±0.2 m/s). Furthermore, AIx decreased by (4.1±0.3%) and SBP reduced by (5±1 mm Hg) (*P*<0.001) after 24 weeks of treatment. London et al 86 investigated the effect of another ACE inhibitor (quinapril) on 12 patients with HTN and ESRD, whereby quinapril therapy caused sustained reduction in PWV, but was dependent on parallel BP reduction. Hence, this effect could be due to the PP reduction and improved aortic distensibility caused by reduced BP.

Angiotensin receptor blockers show an improvement of arterial stiffness according to Klemsdal et al 89 The result demonstrated that PWV declined from 9.3 m/sec to 8.7 m/sec (*P=*0.05) after 4 weeks of treatment with losartan to 16 patients, which can be explained by the direct effect occurs as a result of vasodilation due to smooth muscle relaxation.

Williams et al 96, Boutouyrie et al 97 and Asmar et al 98 investigated combination therapy in three large longitudinal studies with long-term follow-up. The Conduit Artery Function Evaluation (CAFE) study 96, investigated the effect of two combinations of (atenolol with bendroflumethiazide based treatment) and (amlodipine perindopril-based treatment) on the central pressure and stiffness. 2199 patients enrolled in five centres were followed up over 4 years. Office BP readings were the same among both groups, whereas significantly greater reduction in central pressures was observed in the amlodipine/perindopril combination group. The EXPLORE study 97 also compared two groups of drugs combination; amlodipine with valsartan and amlodipine with atenolol. Amlodipine with valsartan showed greater reduction of central pressure than amlodipine with atenolol. In the REASON trial, 98 on subjects with HTN, small dose combination therapy of indapamide (0.625 mg) and perindopril (2 mg) was compared to the effect of 50 mg of atenolol. After 12 months of follow up, the combination dose significantly reduced brachial systolic blood pressure (-6.02 mmHg; 95% CI, -8.90 to -3.14) and PP (-5.57; 95% CI, -7.70 to -3.44) compared to atenolol.

There is no certain therapy to specifically reduce arterial stiffness. However, antihypertensive medications, in particular those with a vasodilatation effect, are likely to be more effective in lowering PWV.

**Conclusion**

It has been proven that there is an acceleration of arterial stiffening in patients with RH. However, the exact mechanisms of this process are not yet fully understood. It has been established that abnormal cfPWV and AIx can serve as markers of TOD and they may help predicting adverse cardiac events. These measures are useful tools for risk stratification in HTN, particularly in its form resistant to treatment. PWV accelerates with age and with the increasing number of cardiovascular factors present in a particular patient. For this reason, this index provides a cumulative characteristic reflective of both physiological age-related risk and an individual chronic exposure to all cardiovascular risk factors. This possibly explains the prominent progression of PWV in RH. Overall, assessment of arterial stiffness provides valuable insight into pathophysiology and prognostication in RH. It may also have a potential as a separate therapeutic target, although this possibility needs further exploration.

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**Figures legends:**

Figure 1. The progression of arterial stiffness exacerbated by the presence of co-morbidities

CV: Cardiovascular; CVD: Cardiovascular Diseases

Figure 2. RH and arterial stiffness share a number of risk factors including, chronic kidney diseases, diabetes mellitus, obesity, female sex, black race and old age

CKD: Chronic Kidney Diseases; DM: Diabetes Mellitus; HT: Hypertension; LVH: Left ventricle hypertrophy; RH: Resistant Hypertension;

**Table 1 PWV Assessments in Resistant Hypertension Population**

| Author/Year | Study Design | Methods | Patients population | Mean age/number | Main Findings in RH |
| --- | --- | --- | --- | --- | --- |
| Vamsi *et al, 2018 44* | Prospective single-centre cohort study | PWV | RH | 58.8\*/80 | **↑** PWV (females vs. males) |
| Niiranen *et* *al*, 201641 | Cross-sectional study | cfPWV | * Uncontrolled treated HTN * Treated HTN | 60/2127 | ↑ PWV in 60% of treated HTN  ↑ PWV in 90% of uncontrolled treated HTN |
| Barbaro *et al, 2015* 43 | Cross-sectional study | * cfPWV * Inflammatory b/m | * RH * Mild HTN * HC | 54.7/72 | ↑ PWV  ↑ inflammatory cytokines  ↑ TNF-𝛼  No differences in IL-6 |
| Barbaro *et al, 2015 42* | Cross-sectional study | * cfPWV * TNF-𝛼 | * RH * HC | 52/51 | ↑ PWV  ↑ TNF-𝛼 |
| Chung *et al, 2014 37* | Observational study | baPWV | * RH * Controlled BP * HC | 65/1620 | ↑ baPWV |
| Faria *et al, 2014*39 | Cross-sectional study | FMD  * cfPWV   Plasma 8-isoprostane | RH  * Controlled HTN | 57/149 | ↑ Plasma 8 isoprostane ↓ FMD ↑ PWV |
| Pabuccu *et al, 2012* 38 | Observational study | * cfPWV * AIx * Aortic strain/US * AD/US | * RH * CHT * HC | 54.7/87 | ↑ AIx  ↑ PWV  ↓ aortic strain  ↓ AD |
| Figueiredo *et al, 2012* 40 | Observational study | * cfPWV * FMD | * RH * Controlled HTN * HC | 52.6/139 | ↓ FMD ↑ PWV |

\*: median age; **AD**: aortic distensibility ; **AIx**: augmentation index; **baPWV**: brachial-ankle pulse wave velocity; **B/M:** biomarker; **BP**: blood bressure; **cfPWV**: carotid-femoral pulse wave velocity; **CAVI**: cardio ankle vascular index; **CBP:** central blood pressure; **CHT:** controlled hypertension; **FMD:** flow-mediated dilatation; **HC**: health control; **HTN**: hypertension; **IL-6**:interleukin-6; **MAP**: mean arterial pressure; **PP**: pulse pressure; **PWV**: Pulse Wave Velocity; **RD**: renal denervation; **RH**: Resistant Hypertension; **TNF:** tumor necrosis factor- 𝛼; **US:** Ultrasound;

**Table 2: Resistant hypertension studies and their fulfilment of criteria to define resistant hypertension as per European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines, 2018**

| Author/ Year | Region | Adherence assessment | **Definition assessment as per (ESH/ESC)** |
| --- | --- | --- | --- |
| Vamsi *et al, 2018 44* | Croatia | \_\_ | √ |
| Barbaro *et al, 2015*43 | Brazil | √ | √ |
| Barbaro *et al, 201542* | Brazil | \_\_ | √ |
| Chung *et al, 2014 37* | China | \_\_ | \_\_ |
| Faria *et al, 201439* | Brazil | √ | √ |
| Figueiredo *et al, 2012*40 | Brazil | \_\_ | √ |
| Pabuccu *et al, 2012* 38 | Germany | \_\_ | √ |

**Table 3 Impact of Antihypertensive Drugs on Arterial Stiffness**

| Author/ Year | Treatments | Patients population | Sample size | Follow-up | Effect on brachial SBP | Effect on PWV | Effect on central SBP | Effect on AIx |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Asmar *et al, 2001* 98 | Indapamide+Perindopril vs Atenolol | HTN | 471 | 12 months | ↓ Ind/Per | similar reduction | ↓ Ind/Per | ↓ Ind/Per |
| Hirata *et al, 2005* 95 | Ramipril vs Atenolol vs Placebo | patients with coronary risk factors | 30 | Measurements repeated every  30-60 min/5h on 3 separate days within ≥7 days | ↓ Ramipril | similar reduction | ↓ Ramipril | ↓ Ramipril |
| London *et al,1996* 86 | Quinapril vs Placebo | HTN+ESRD | 12 | After 127h of drug administration | ↓ | ↓ | ↓ | ↓ |
| Klemsdal *et al, 1999* 89 | Losartan vs Placebo | HTN | 16 | 4 weeks | ↓ | ↓ | ↓ | - |
| Davies *et al, 2005* 88 | Spironolactone vs Placebo | HTN+DM | 10 | 4 months | ↓ | ↓ | - | - |
| Williams *et al, 2006* 96 | Atenolol+Thiazide  vs  Amlodipine+Perindopril | HTN | 2119 | 4 years | similar reduction | similar reduction | ↓ Aml/Per | ↓Aml/Per |
| Boutouyrie *et al, 2010* 97 | Amlodipine+Valsartan  vs  Amlodipine+Atenolol | HTN | 393 | 24 weeks | similar reduction | similar reduction | ↓Aml/Vals | ↓Aml/Vals |

**Aml/Per:** Amlodipin and Perindoprilcombination**; Aml/Vals:** Amlodipine and Valsartan combination; **ESRD**: End stage renal disease; **HTN:** Hypertension; **Ind/Per**: Indapamide and Perindopril combination; **PAD:** Peripheral artery diseases; **DM:** Diabetes mellitus; ↓:Significant reduction;

Icon

Description automatically generated with low confidence

Figure 1.

Diagram

Description automatically generated

Figure 2.