# Studies on blood pressure variability and pathogenic mechanisms of cardiovascular risk in secondary hypertension

# Chapter 8

# Summary and Perspectives

This thesis, in the first part, demonstrates that secondary hypertension forms, including those with lower prevalence (i.e., pheochromocytoma/paraganglioma – PPGLs and fibromuscular dysplasia – FMD), are characterised by a wide spectrum of hypertension-associated aspects, such as increasing of blood pressure variability (BPV) and sleep disorders risk that should be considered during the overall clinical work-up. Inexpensive and broadly available instruments such as 24-h ambulatory blood pressure monitoring (ABPM) and sleep questionnaires (i.e., STOP-Bang, Insomnia Severity Index, and Restless Legs Syndrome Rating Scale) are helpful to assess additional 'clues' for diagnosing and for stratifying cardiovascular risk in these patients.

The second part of the research focused on a widespread form of secondary hypertension, obstructive sleep apnoea (OSA). I searched how it could be screened by a simple validated questionnaire (i.e., STOP-Bang) in hypertensive patients with higher cardiovascular risk and what are the biochemical mechanisms involved in its association with hypertension (HT) and cardiovascular diseases development.

***Blood pressure variability assessment***

The assessment of short-term BPV by 24-h ABPM is an easy, inexpensive, and validated instrument[1,2] that should become a part of the management of primary and secondary hypertensive patients. Several studies, in fact, have demonstrated that increased BPV markers recorded by 24-h ABPM are associated with a greater risk of hypertension-mediated organ damage (HMOD) and cardiovascular complications.[3,4] Many causes have been considered in the pathogenesis of altered BPV among those the sympathetic nervous system (SNS) activation and the hormonal dysfunction.[2,5]

In patients affected by pheochromocytoma and paraganglioma, we observed an impressive decrease of BPV indexes after surgically tumours removal (**CHAPTER 2**). In these patients, it is feasible that the persistent or pulsatile oversecretion of plasma epinephrine and norepinephrine (dopamine also but on a smaller scale) causes sympathetic hypertone, a saturation of adrenergic receptors, and the development of increased BPV.[6] In our study, although BPV was not significantly associated with vascular remodelling and renal dysfunction, we underlined that in PPGLs patients BPV assessment should represents an additional instrument: (i) to suspect the presence of catecholamine-producing tumour, even when the plasma catecholamines and/or the urinary metanephrines result into the normal range; (ii) to evaluate the efficacy of surgical tumour removal and promptly recognise eventual recurrences of disease.

In our study, BPV was not significantly associated with vascular remodelling and renal dysfunction. However, we underlined that in PPGLs patients, BPV assessment should represent an additional instrument: (i) to suspect the presence of catecholamine-producing tumour, even when the plasma catecholamines and/or the urinary metanephrines result into the normal range; (ii) to evaluate the efficacy of surgical tumour removal and promptly recognise eventual recurrences of the disease.

The importance of BVP assessment is also remarked for FMD hypertensive patients (**CHAPTER 3**). In this relatively rare form of secondary hypertension, we found that for those with exclusive renal artery involvement, the BPV markers were higher than FMD patients with multivessel localisation. Moreover, the active plasma renin concentration measured in the renal artery blood samples correlates significantly with the main BPV markers, such as systolic BP weighted standard deviation and the average real variability. However, our findings could be affected by two main reasons: in the renal artery FMD group we found the presence of a significantly greater rate of unifocal renal disease, which has been demonstrated to be associated with a worse prognosis, and the administration of peripheral α-blockers that can induce orthostatic hypotension. Despite all limitations, this is the first research performed aimed to evaluate the BPV profile in FMD patients. FMD is characterised by irreversible non-inflammatory and non-atherosclerotic destructuring of medium- and large-size artery walls.[7] Apparently, without specific aetiology, these anatomic alterations arise mostly in young - adult females, and, when it determines critical stenosis or large aneurisms, could be fatal if not promptly recognised.[7] Additionally, in the renal artery involvement, often, a secondary severe, malignant, and 'difficult-to-treat' form of HT develops (among patients with renovascular hypertension its incidence is about 10%).[7,8] These subjects, thereby, show an increased cardiovascular risk compared to normotensive and primary hypertensive patients. The increased BPV might represent an additional risk factor. Further prospective designed and larger studies are impelling to confirm my assumption.

The association between BPV and chronic kidney disease (CKD) has been already ascertained. It has been determined as well that higher BPV values can contribute to renal impairment progression not only in diabetic CKD patients but also in normotensive subjects.[9-11] However, the role of sleep fragmentation in these subjects has not been deeply investigated. The analysis of BPV during the night performed in patients affected by OSA, confirmed that sleep fragmentation causes an increase of BPV probably due to recurrent awakes from sleep, arterial blood desaturations, and SNS activation.[12] Sleep

disorders and OSA are widespread in CKD;[13,14] higher potassium levels, hypocalcaemia and secondary hyperparathyroidism, altered glucidic metabolism, high values of uremic acids, and volume overload are just part of the main complex mechanisms involved in this association. The most common sleep disorders, insomnia, restless legs syndrome, and OSA, can be screened by validated questionnaires when the suspect is high, as in the case of CKD patients. These questionnaires represent a simple, inexpensive, and easy to compile instrument that contains much information. The Insomnia Severity Index (ISI),[15] with a cut-off >10, has adequate internal consistency and is a reliable self-report measure to evaluate perceived sleep difficulties. The Restless Legs Syndrome (RLS) Rating Scale was developed by the International Restless Legs Syndrome Study Group and, similarly to the ISI questionnaire, it meets performance criteria for a brief, patient completed instrument that can be used to assess RLS severity for purposes of clinical and therapeutic assessment.[16] Lastly, the STOP-Bang questionnaire was developed by anaesthesiologists to assess pre-operative OSA risk.[17,18] With a range score from 0 to 8, this questionnaire can be completed quickly and easily (usually within 1-2 min), and it demonstrated a high sensitivity using a cut-off score of ≥3: 84% in detecting any sleep apnoea (AHI >5 events/h), 93% in detecting moderate-to-severe OSA (AHI >15 events/h), and 100% in detecting severe form (AHI >30 events/h).[17] Hence, the STOP-Bang questionnaire can be considered a validated screening tool. Based on these observations, with our study (**CHAPTER 4**), we demonstrated that not only does the exclusive assessment of BPV have an essential role in the stratification of cardiovascular risk in CKD patients, but also the screening for the most frequent sleep disorders because they can impact significantly on BPV profile. We enlighten that there was a strict association between insomnia risk (ISI >14) and RLS (RLS Rating Scale >10) and systolic and diastolic nocturnal BPV, respectively. Thus, sleep questionnaires might be managed by every clinician and should be available in all specialised centre for the management of HT, because they offer a simple method to: (i) evaluated additional cardiovascular risk factors, (ii) diagnose those patients with high sleep disorders risk, which need to further investigation, (iii) introduce a proper treatment with the aim to reduce cardiovascular risk.

***Sleep disorders screening***

The same questionnaires before mentioned have been used to screen sleep disorders in young-adult hypertensive patients with primary and secondary hypertension, referred to our specialised centre to manage HT at the University of Padova. Increasingly evidence

shows a direct link between sleep disorders and the development of hypertension, HMOD, and cardiovascular complications.[19] Data about insomnia, RLS, and cardiovascular diseases is emerging[20,21] and still defining,[19] whereas the association with OSA has been well established.[22] Specifically, OSA patients with moderate-to-severe disease, compared with the hypertensive non-OSA population, show increased rate of left ventricular hypertrophy[23,24] and urinary albumin excretion.[25] With our research (**CHAPTER 5**), we confirmed the evidence of cardiac remodelling in higher OSA risk patients (STOP-Bang ≥3), and we found a significant correlation between STOP-Bang score and left ventricular mass index, left atrial and aortic root enlargements. Hence, we demonstrated that a simple validated questionnaire for OSA screening could identify the increased heart damage in primary and secondary hypertensive patients. Accordingly, when the poor access to specialised, expensive, and time-consuming instruments limits the proper diagnosis of sleep disorders, these results enlighten the usefulness of simple questionnaires as screening tools in managing the hypertensive population.

***Pathogenesis of the association between obstructive sleep apnoea and cardiovascular disease***

OSA affects millions of people and is considered a worldwide health problem.[26] However, the underlying mechanisms that associate this condition to HT and cardiovascular complications are very complex, involve multiple systems, and have been not completely understood. For this reason, in **CHAPTERS 6** and **7**, I described the protocol and the preliminary results of a study designed with the aim to analyse the SNS and renin-angiotensin-aldosterone system (RAAS) activation and endothelial dysfunction.[22] My current results highlight significant changes in the catechol-O-methyltransferase (COMT) activity, a key enzyme that metabolises plasma catecholamines.[27] Giving its effect on all molecules with catechol-group, including dopamine, it has been extensively studied for the treatment of Parkinson's disease.[28] However, less is learned about its role in catecholamine metabolism with regards to the development of HT and other cardiovascular disorders. Thus, I tried (i) to demonstrate that during the apnoea patients with OSA exhibit the activation of the catecholaminergic system, and (ii) to understand whether COMT activity was triggered by plasma catecholamines secretion, hypoxia, and/or plasma endothelin-1. From a purely pathophysiological perspective, this study sheds some light on the biochemical mechanisms that cause an increase in catecholamines levels in OSA patients, and it might

lay the foundation for specific molecular-target treatments. On the other hand, from the clinical perspective, it could help clinicians understand which patients with OSA are more suitable to develop HT and cardiovascular events and who might benefit the most from the treatment.

In conclusion, this thesis demonstrates that associated aspects of arterial hypertension should be evaluated, such as blood pressure variability and sleep disorders, in secondary hypertension as well. Furthermore, this thesis provides new perspectives on potential pathogenic systems involved in the strict relationship between OSA, hypertension and cardiovascular diseases.