Current Hypertension Reports (2019) 21: 90
https://doi.org/10.1007/s11906-019-0989-9

SECONDARY HYPERTENSION: NERVOUS SYSTEM MECHANISMS (M WYSS, SECTION EDITOR)

Pheochromocytoma as a Clinical Model of Peripheral Sympathetic Overdrive: Old and New Findings

Guido Grassi[1] · Fosca Quarti Trevano[1] · Raffaella Dell'Oro[1] · Gino Seravalle[1] · Giuseppe Mancia[2]

Published online: 10 October 2019

Abstract

Purpose of Review The present paper will review the results of experimental and clinical studies aimed at defining the functional behavior of the central and peripheral nervous system in adrenal pheochromocytoma.

Recent Findings The contribution of sympathetic neural influences to the development of high blood pressure values in pheochromocytoma is complex. Studies performed in experimental animal models have shown that hypertension and the concomitant high circulating levels of catecholamines can lead to inhibition of central sympathetic neural outflow by reflex mechanisms and direct stimulation of central adrenergic receptors, respectively. However, these studies have also shown that high circulating levels of catecholamines favor a downregulation of alpha- and beta-adrenergic receptors, lessening their response to endogenous and exogenous adrenergic stimulation. The present paper reviews results of human studies performed by our group and others on the behavior of the central and peripheral nervous system in human pheochromocytoma. We discuss data collected in patients with different levels of peripheral sympathetic drive, i.e., before and after surgical removal of the adrenal pheochromocytoma.

Summary In the presence of elevated plasma catecholamine level, such as that characterizing adrenal pheochromocytoma, microneurography shows that central sympathetic neural activity is normal or even inhibited. At the peripheral vascular level, pheochromocytoma is characterized by a reduced vascular reactivity to exogenous sympathetic stimulation but a normal response by the vessels to endogenous adrenergic stimulation.

Keywords Secondary hypertension · Pheochromocytoma · Sympathetic activity · Reflex control of the cardiovascular system · Adrenergic receptors

Introduction

There are several important reasons for the current interest in pheochromocytoma by clinical and basic researchers. First, research into this rare but clinically relevant secondary form of hypertension has provided critical data on catecholamine metabolism and function. Second, pheochromocytoma represents a unique "model" of selective, chronic neuroadrenergic stimulation, which mainly involves the adrenal glands and the peripheral sympathetic nervous system [1••], in contrast to other hypertension conditions primarily characterized by the presence of a central nervous system sympathetic overdrive, such as essential hypertension and congestive heart failure [2•, 3•]. Finally, since pheochromocytoma can be successfully cured by surgical interventions, this "model" of chronic peripheral adrenergic activation appears to be reversible. This feature facilitates investigation of the neuroadrenergic cardiovascular drive before and after the removal of the tumor, thus at different functional circulating plasma catecholamine levels. This indicates that pheochromocytoma can be regarded as a unique model of reversible hypertension with peripheral neuroadrenergic overactivity.

This paper reviews current knowledge of the behavior of the central sympathetic nervous system regulation of the cardiovascular system in pheochromocytoma and discusses the results obtained by our group and others, which employed sophisticated approaches to assess central sympathetic outflow in humans, such as the microneurographic technique. It

This article is part of the Topical Collection on *Secondary Hypertension: Nervous System Mechanisms*

✉ Guido Grassi
guido.grassi@unimib.it

[1] Clinica Medica, Department of Medicine and Surgery, University of Milano-Bicocca, Via Pergolesi 33, 20052 Monza (Milan), Italy

[2] University of Milano-Bicocca, Milan, Italy

also examines the functional status of peripheral sympathetic drive at the vascular level, by reporting the results of studies performed by our group, which looked at the vascular responses to homologous (or endogenous) and heterologous (exogenous) sympathetic stimulation. It is worth mentioning that in both the abovementioned studies, the results are based on the functional evaluation of the adrenergic nervous system before and after surgical removal of the chromaffin neoplastic tissue, allowing collection of functional data at different circulating norepinephrine and epinephrine plasma levels. The clinical implications of these findings will be highlighted briefly.

Pathophysiological Background

Pheochromocytoma is a tumor of the chromaffin cells anatomically located within the sympathoadrenal tissue, which is capable of synthesizing biologically active compounds, such as norepinephrine and epinephrine. Frequently, although not invariably, tumors located in the adrenal glands preferentially release epinephrine, while extra-adrenal pheochromocytomas store and release both catecholamine types. While in physiological conditions secretion of catecholamines is under central neural regulation, in the case of the presence of the tumor, this process appears independent on the central neural influences, presumably because the chromaffin tissue in is not innervated [4]. The specific clinical picture of the tumor, which consists of stable or paroxysmal hypertension, tachycardia, cardiac rhythm disturbances, glucose intolerance, excessive and generalized sweating, and orthostatic hypotension, is generally dependent on the adverse cardiovascular and metabolic effects of high catecholamine levels [1••, 5•]. From a cardiovascular viewpoint, for example, the occurrence of tachycardia at rest and the development of cardiac rhythm disturbances depend respectively on the positive chronotropic and proarrhythmogenic effects of norepinephrine and epinephrine on myocardial tissue [1••, 5•]. On the other hand, from a metabolic viewpoint, the increased plasma glucose levels largely depend on the stimulating effects exerted by both catecholamines on glucogenesis and gluconeogenesis [6••]. Furthermore, both catecholamines are capable of triggering remarkable increases in blood pressure levels which are dependent both on the vasoconstrictive properties of norepinephrine (mediated by alpha-1 adrenoreceptor stimulation) and on the systolic blood pressure elevation mediated by the epinephrine-dependent tachycardia [1••, 5•]. Finally, postural hypotension has been ascribed to the decrease in circulating blood volume and/or to a hypothesized impairment of reflex mechanisms regulating blood pressure values [7] (see below). Altogether these effects explain the clinical complexity of the disease, which has been regarded in the past for the heterogeneity of its manifestations as the "great mimic."

Behavior of Central Sympathetic Function in Pheochromocytoma

Defining the behavior of the central nervous system in patients with pheochromocytoma may have important pathophysiological and clinical implications. One of them is represented by the evidence that direct and reflex stimulation of the central nervous system may be responsible in patients with pheochromocytoma for the occurrence of hypertensive crises [6••]. In addition, occurrence of central sympathetic stimulation in these patients explains the occurrence of acute blood pressure increases without further elevation in plasma catecholamine levels, as not infrequently happens in current clinical practice [1••, 8]. Finally, the presence of a central sympathetic stimulation associated with elevated peripheral adrenergic overdrive represents the background for employing centrally acting drugs for lowering blood pressure in this clinical condition before the surgical removal of the tumor [1••, 6••].

Results of different studies suggest that the sympathetic outflow from the central nervous system should be almost unaffected or even enhanced by the presence of pheochromocytoma [9, 10]. It has been, for example, shown that in rats harboring a transplantable pheochromocytoma, secreting norepinephrine as well as dopamine clonidine administration, i.e., a drug acting on the central nervous system, triggers a blood pressure reduction of a marked degree similar in magnitude to the one detected in spontaneously hypertensive rats with a marked increase in central sympathetic activity [11]. Furthermore, evidence has been provided that in patients with pheochromocytoma, reflex sympathetic control of the cardiovascular system exerted by different reflexogenic areas, such as the arterial baroreflex, the cardiopulmonary reflex, and the chemoreflex, is functionally normal [12•]. In addition, clonidine administration significantly lowers in patients with a pheochromocytoma and elevated blood pressure and heart rate values without substantially modifying the high circulating plasma levels of catecholamines secreted by the tumor throughout its central sympathoinibitory effects [9]. Finally, patients with a secondary hypertension due to pheochromocytoma display at the 24-h ambulatory blood pressure monitoring a marked attenuation of the fall in blood pressure values recorded during sleep in the nighttime period, a finding that again points toward the presence of a "supranormal" central sympathetic drive [13].

We had the chance to reexamine the central neurogenic contribution in pheochromocytoma by performing sympathetic nerve traffic recordings in the peroneal nerve in patients with an adrenal form of this tumor [14]. The unique features of this study were represented by (1) the use of the microneurographic technique allowing to precisely quantify efferent postganglionic sympathetic nerve traffic, which represents a faithful marker of central adrenergic drive [12•] and (2) the study design, approved by the ethics committee of the

institutions involved, which included two experimental sessions, one performed 4–6 days before the surgical intervention and the second 51 to 94 days after surgery. In both instances, the patients were hospitalized to safely and properly assess via microneurography sympathetic nerve traffic together with the other hemodynamic and biochemical variables including venous plasma norepinephrine and epinephrine. The main results of the study, which was performed in 6 patients with an adrenal pheochromocytoma with a mean age of 49.3 years, are shown in Fig. 1. Surgical removal of pheochromocytoma induced a significant marked reduction in both plasma norepinephrine and epinephrine values, which was accompanied by a clear-cut decrease in clinic systolic and diastolic blood pressure as well as in heart rate. More importantly, efferent postganglionic muscle sympathetic nerve traffic showed a significant increase after surgery, both when expressed as burst incidence over time (bursts/min) and as burst incidence corrected for heart rate (bursts/100 heart beats). This finding may suggest that in pheochromocytoma, central sympathetic nerve traffic undergoes an inhibition by the elevated circulating plasma levels of catecholamines produced by the tumor and that a restoration of normal sympathetic central outflow may occur when norepinephrine and epinephrine synthesis returns to normal, i.e., after surgery. It thus appears that in contrast to what has been previously discussed as evidence of a normal (or even augmented) central sympathetic neural drive, pheochromocytoma is characterized by a central sympathoinhibition. Although the results of these studies are difficult to be reconciled with each other in a unifying hypothesis, two important study limitations should be emphasized.

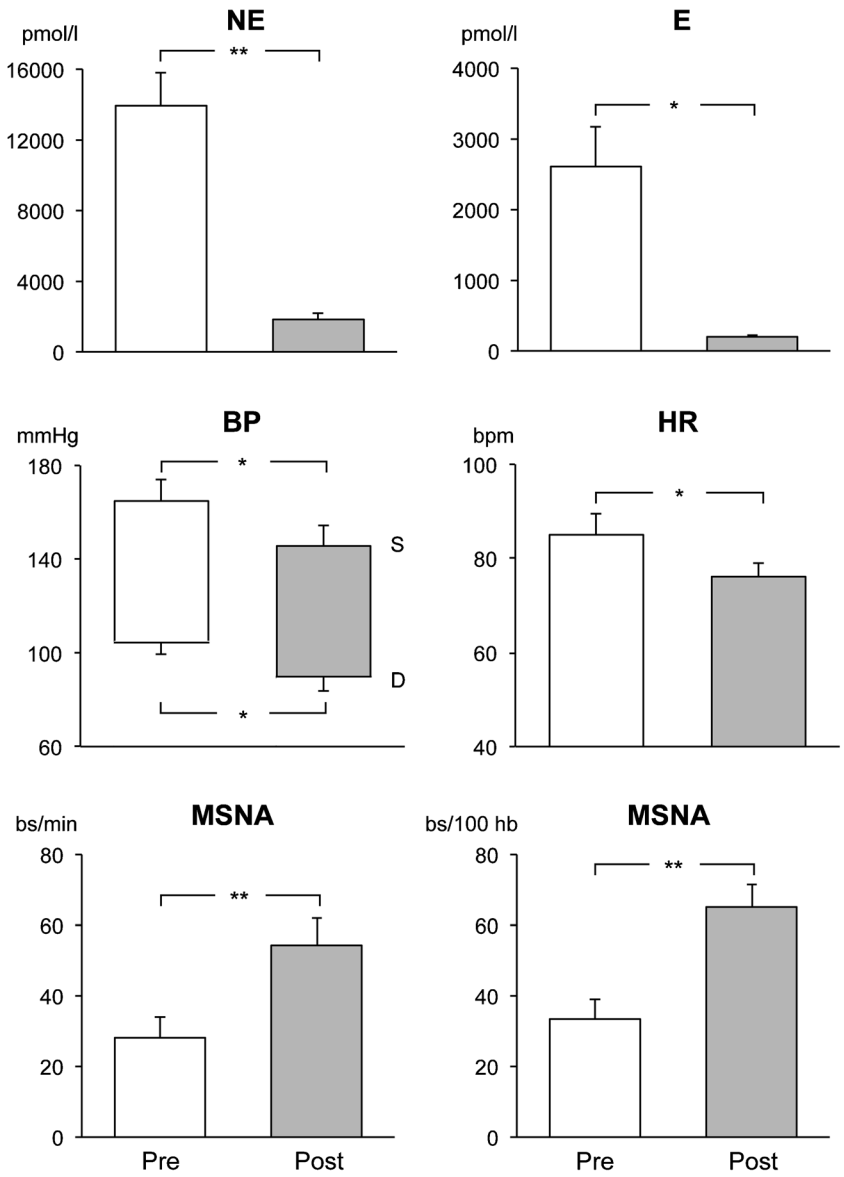

Fig. 1 Bar graphs showing venous plasma norepinephrine (NE), plasma epinephrine (E), systolic (S) blood pressure (BP), diastolic (D) blood pressure (BP), heart rate (HR), and efferent postganglionic muscle sympathetic nerve activity (MSNA), expressed as bursts/minute (bs/min) and as bursts corrected for heart rate (bursts/100 heart beats (bs/100hb)) in 6 patients with an adrenal pheochromocytoma before (open bars) and about 2 and a half months after (dashed bars) surgical removal of the tumor. Data are shown as means ± standard errors. Asterisks (*$P < 0.05$, **$P < 0.01$) refer to the statistical significance of the values recorded before (pre-) and after (post) surgery. Figure drawn from data presented as table in 14

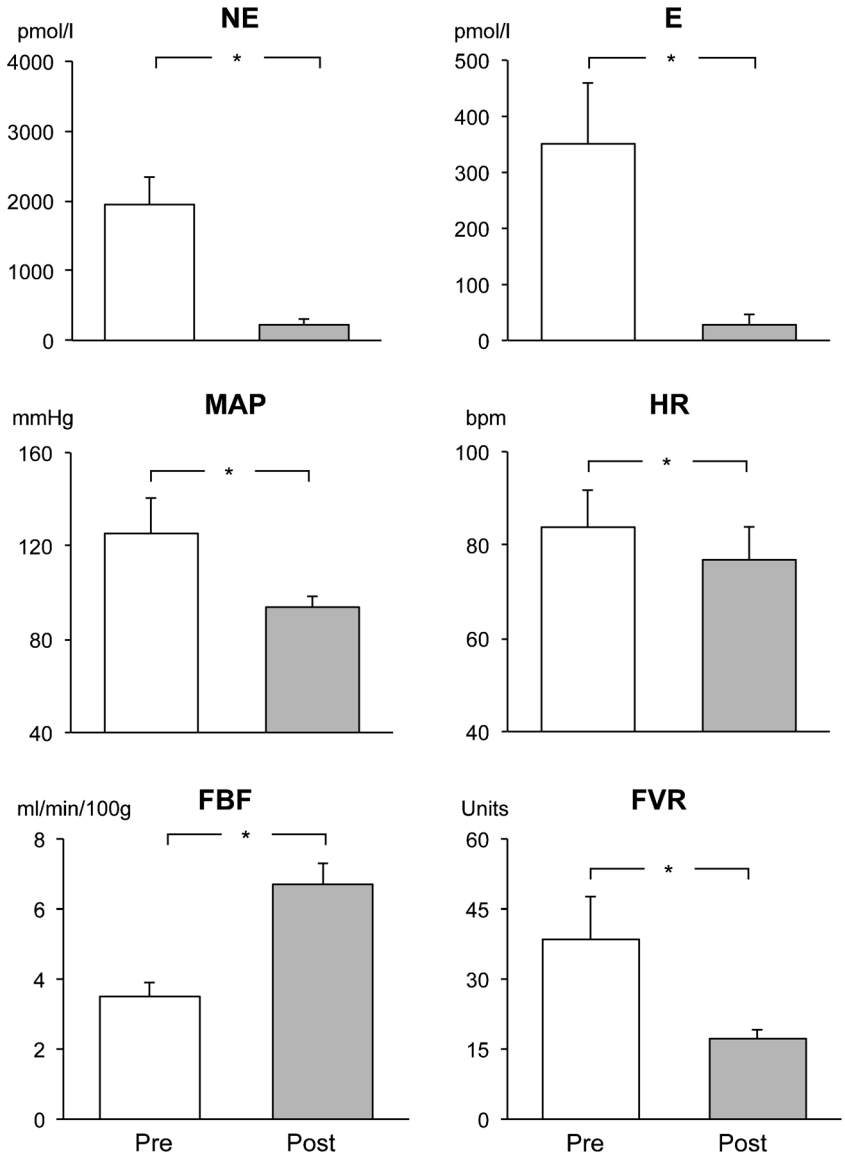

Fig. 2 Bar graphs showing venous plasma norepinephrine (NE), plasma epinephrine (E), mean arterial pressure (MAP), heart rate (HR), forearm blood flow (FBF, venous occlusion plethysmography), and forearm vascular resistance (FVR) in 6 patients with an adrenal pheochromocytoma before (open bars) and about 2 months after (dashed bars) surgical removal of the tumor. Data are shown as means ± standard errors. Asterisks (*$P < 0.05$, ** $P < 0.01$) refer to the statistical significance of the values recorded before (pre-) and after (post) surgery

First, it is difficult to compare the results of the different studies performed in pheochromocytoma because frequently profound differences occur between study populations as far as the predominance of different catecholamine release is concerned. In particular, some patients predominantly secrete epinephrine, others norepinephrine, and additional others both the two catecholamines. This appears to be important given the substantial differences these two adrenergic neurotransmitters may have on the central nervous system and on the cardiovascular function as well [4, 15]. Second, because the microneurographic technique allows only at investigating central sympathetic neural outflow to the skeletal muscle district, it is difficult to generalize the results of these studies to other regional areas, such as the coronary, the cerebral, or the renal circulation, which frequently display a behavior heterogeneous and dissimilar from the one seen in the muscle vascular one [16••]. Only studies based on regional norepinephrine radiolabeled spillover technique [4, 16••] will allow in the future at clarifying this still controversial and intriguing issue.

Behavior of Peripheral Sympathetic Function in Pheochromocytoma

Studies performed in rats harboring pheochromocytoma have shown that the pressor responses to alpha-adrenergic agonists are attenuated, and this phenomenon is progressively more pronounced as the time after pheochromocytoma transplantation increases [17]. In the early stages after the tumor implantation, the phenomenon is selective for the exogenous administration of the alpha-adrenergic receptor agonist norepinephrine while at a later stage, i.e., 6 to 7 weeks after the tumor

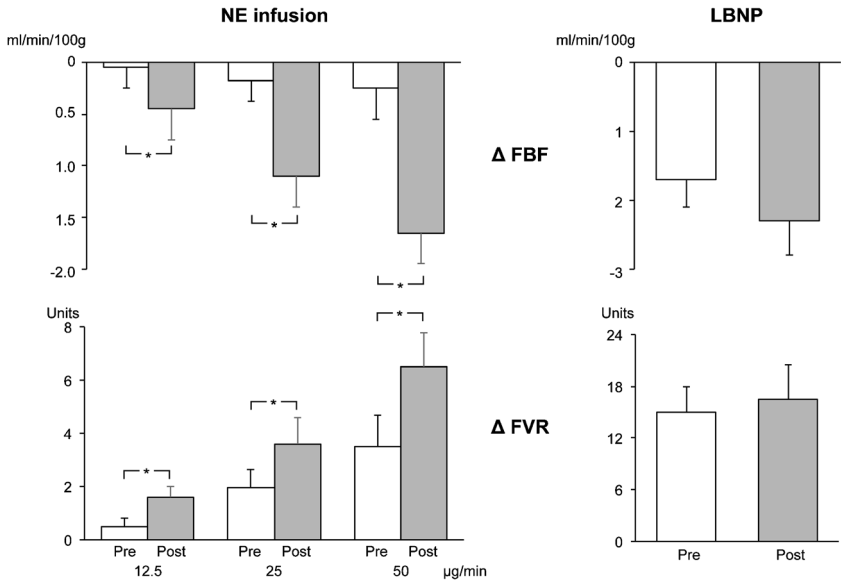

Fig. 3 Progressive reductions in forearm blood flow (ΔFBF) and progressive increase in forearm vascular resistance (ΔFVR) induced by intravenous infusion of norepinephrine at increasing doses (NE infusion, left panels) and by a mild degree of lower body negative pressure (LBNP, right panels) in 6 patients with a pheochromocytoma before (pre-) and after (post) surgical removal of the tumor. Data are shown as absolute mean ± standard error changes compared with baseline values (shown in Fig. 2). Asterisks (*$P < 0.05$) refer to the statistical significance of the values recorded before (pre-) and after (post) surgery

transplantation; this is the case also for the vasoconstrictor responses to non-adrenergic substances such as vasopressin and angiotensin II [17]. This functional adrenergic receptor desensitization is accompanied by a downregulation in receptor subtypes, with a consistent decrease (about 70%) in the number of alpha-1 adrenergic receptors anatomically located in the membranes of cells in the kidneys and lungs [18]. The results of these studies have been confirmed also in humans, with the evidence that in pheochromocytoma patients, the elevated circulating levels of norepinephrine markedly impair the forearm blood flow vasodilatation induced by infusion of acetylcholine, which is mainly mediated by the endothelium [19, 20, 21•]. This behavior is in sharp contrast with the one seen during administration of isosorbide dinitrate, which triggers a forearm vasodilatation independent on nitric oxide production and thus not mediated by the endothelium [19, 20, 21•]. It thus appears that in pheochromocytoma, catecholamines selectively impair endothelium- mediated vasodilatation [22]. This conclusion was confirmed, in the abovementioned study [19], by the finding that an almost complete normalization of the vascular responses to acetylcholine was obtained in the same patients 4 weeks after the surgical removal of pheochromocytoma.

The abovementioned findings, although of major importance for clarifying the nitric oxide/sympathetic interactions in pheochromocytoma, do not allow at determining two aspects of major relevance in the pathophysiology of the disease. First is whether the downregulation of the adrenergic

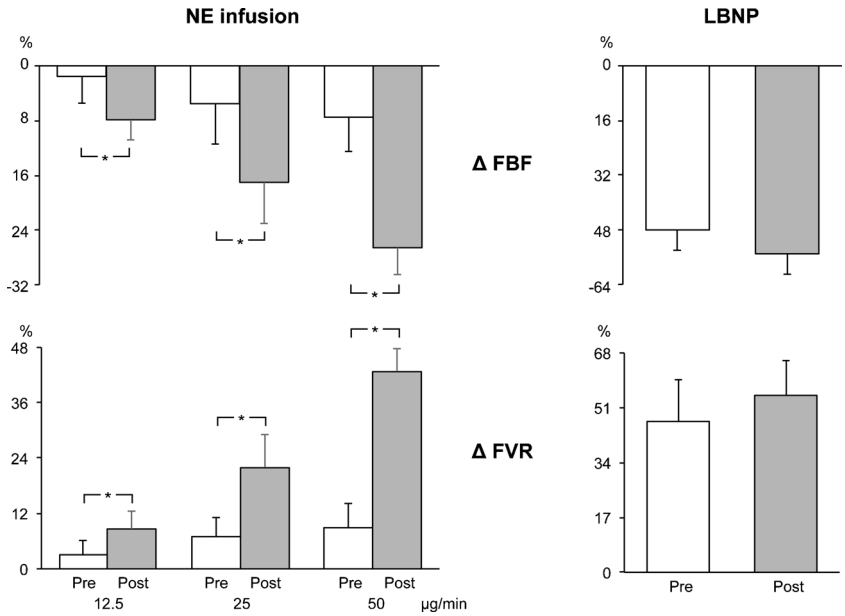

Fig. 4 Progressive reductions in forearm blood flow (ΔFBF) and progressive increase in forearm vascular resistance (ΔFVR) induced by intravenous infusion of norepinephrine at increasing doses (NE infusion, left panels) and by a mild degree of lower body negative pressure (LBNP, right panels) in 6 patients with a pheochromocytoma before (pre-) and after (post) surgical removal of the tumor. Data are shown as percent (means ± standard errors) changes compared with baseline values (shown in Fig. 2). Asterisks (*$P < 0.05$) refer to the statistical significance of the values recorded before (pre) and after (post) surgery

receptors is a phenomenon which can be selectively detected for the exogenous stimulation of the sympathetic function only or rather it also affects the endogenous "neurogenic" one. The issue appears to be of major clinical relevance because the occurrence of a generalized functional desensitization affecting both endogenous and exogenous adrenergic stimulation may imply that functional homeostasis is almost lost in the disease. An additional intriguing question is whether the functional adrenergic desensitization is a phenomenon which can be favorably affected by surgical removal of pheochromocytoma or in contrast it is irreversible.

To address the two abovementioned questions, we evaluated patients with a documented adrenal pheochromocytoma, with an age amounting to 34.8 ± 4.6 years [23]. In each patient, we measured throughout high-performance liquid chromatography venous plasma norepinephrine and epinephrine levels along with clinic blood pressure and heart rate values. Measurements also included forearm blood flow, as assessed throughout venous occlusion plethysmography, and forearm vascular resistance (mean arterial pressure divided by forearm blood flow). All measurements were obtained at rest and during (1) exogenous adrenergic stimulation via stepwise intravenous infusion of norepinephrine (5–50 μg/min) and (2) endogenous sympathetic stimulation reflexly induced by producing via a mild degree of lower body negative pressure a reflex forearm vasoconstriction mediated by the deactivation of cardiopulmonary volume receptors [7]. The unique feature of the study, which was approved by the ethics committees of the institutions involved, consisted in the collection of the abovementioned adrenergic vascular responses at baseline and then about 2 months after successful surgical removal of pheochromocytoma. The main study findings can be summarized as follows. First, as shown in Fig. 2, the surgical removal of the adrenal tumoral mass induced, as expected, a significant and marked reduction in venous plasma norepinephrine and epinephrine levels, with a complete normalization of their circulating values. This was accompanied by a significant reduction in systolic and diastolic blood pressure, together with a significant decrease in heart rate. Forearm blood flow values significantly increased while forearm vascular resistance significantly decreases, indicating the occurrence of a marked peripheral vasodilatation. Norepinephrine stepwise infusion elicited, as expected, a progressive reduction in forearm blood flow and a specular progressive increase in forearm vascular resistance (Fig. 3, left panels). The vascular responses to exogenously administered norepinephrine were markedly and significantly potentiated after the surgical removal of pheochromocytoma, suggesting that in the pre-surgery condition, there was a downregulation of alpha-1 vascular adrenoreceptors which was almost completely reversed after surgery, when a normalization of catecholamine production occurred. In contrast, the vascular responses to endogenous reflex adrenergic stimulation were similar in magnitude before and after the surgical procedure (Fig. 3, right panels), suggesting that the functional downregulation of the alpha-adrenergic receptors selectively affects exogenous sympathetic stimulation only. The results were similar when the data were expressed as percent rather than as absolute values (Fig. 4). It can be thus concluded that in pheochromocytoma, the vascular adrenergic receptor downregulation affects quite selectively the responses to exogenous sympathetic stimulation (infusion of norepinephrine) and that no such phenomenon does occur for endogenously produced norepinephrine, such as that triggered by reflex stimuli (lower body negative pressure).

Conclusions

Pheochromocytoma is characterized by complex functional modifications of both the central and peripheral sympathetic nervous system, which include both central and peripheral alterations. Both these neuroadrenergic abnormalities appear to be reversible with surgery. Many questions remain, however, about the behavior of peripheral as well as central sympathetic function in pheochromocytoma. They include the following:

- Is the behavior of the central sympathetic neural drive different in pheochromocytomas predomitantly secreting epinephrine vs those mainly producing norepinephrine?
- Is the adrenergic receptor desensitization a phenomenon peculiar of pheochrocytoma predomitantly secreting norepinephrine?
- What is the time course of the process leading to a restoration of a normal vascular adrenergic reactivity after surgical treatment?
- Are paragangliomas characterized by adrenergic alterations similar to the ones described in pheochromocytoma?
- Do the metabolic effects of the tumoral chromaffin cells on glucose metabolism and insulin sensitivity participate at the vascular adrenergic desensitization?
- Are paroxismal pheochromocytoma forms "sympathetically" different from the ones characterized by a stable hypertensive state?

Future studies are thus recommended to address the abovementioned questions, which, as previously emphasized, are relevant not only for better understanding the variegated pathophysiology of pheochromocytoma but also for improving the clinical outcome of the disease and its management.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflict of interest relevant to this manuscript.

Human Rights and Informed Consents This article includes data of clinical studies performed by the authors of this manuscript with human subjects, whose protocol has been approved by the ethics committees of

the institutions involved. Animal studies mentioned in the text have not been performed by any author of the present paper.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Landsberg L, editor. Pheochromocytomas, paragangliomas and disorders of the sympathoadrenal system. Cham: Springer International Publishing; 2018. p. 1–212. **An update and comprehensive review of different clinical forms of pheochromocytoma.**

2.• Grassi G, Pisano A, Bolignano D, Seravalle G, D'Arrigo G, Quarti-Trevano F, et al. Sympathetic nerve traffic activation in essential hypertension and its correlates: systematic reviews and meta-analyses. Hypertension. 2018;72:483491. https://doi.org/10.1161/hypertensionAHA.188.11038 **The results of the meta-analysis provide conclusive evidence based on more than 60 microneurographic studies on the main feature of the sympathetic activation characterizing essential hypertension.**

3.• Grassi G, D'Arrigo G, Pisano A, Bolignano D, Mallamaci F, Dell'Oro R, et al. Sympathetic neural overdrive in congestive heart failure and its correlates: systematic reviews and meta-analysis. J Hypertens. 2019;37:1746–56. https://doi.org/10.1097/HJH.0000000000002093 **The results of the meta-analysis provide conclusive evidence based on more than 100 microneurographic studies on the main feature of the sympathetic activation characterizing mild and severe congestive heart failure.**

4. Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate and functions. Physiol Rev. 1990;70:963–85. https://doi.org/10.1152/physrev.1990.70.4.963.

5.• Gu YW, Poste J, Kunal M, Schwarcz M, Weiss I. Cardiovascular manifestations of pheochromocytoma. Cardiol Rev. 2017;25:215–22. https://doi.org/10.1097/CRD.0000000000000141 **An update review of common and uncommon cardiovascular effects of pheochromocytoma.**

6.•• Lenders JW, Duh QF, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99:1915–42. https://doi.org/10.1210/jc.2014-1498 **A state-of-the-art document on the diagnostic and therapeutic recommendations for pheochromocytoma management.**

7. Seravalle G, Grassi G. Cardiovascular physiology: regulation of blood pressure. In: Camm AJ, Luscher TF, Maurer G, Serruys PW, editors. The ESC Textbook of Cardiovascular Medicine. Oxford: Oxford University Press; 2018. p. 126–34.

8. Januszewicz A, Lenders JWM, Eisenhofer G, Prejbisz A. Pheochromocytoma and paraganglioma. 3rd edition. In: Mancia G, Grassi G, Tsoufis KP, Dominiczak AF, Agabiti Rosei E, ed. Florida: CRC Press; 2019. p. 523–531.

9. Bravo E, Fouad-Tarazi F, Rossi G, Imamura M, Lin WW, Madkour MA, et al. A reevaluation of the hemodynamics of pheochromocytoma. Hypertension. 1990;15(suppl 2):1128–31. https://doi.org/10.1161/01.hyp.15.2_suppl.i128.

10. Bravo EL, Tarazi RC, Fouad FM, Textor SC, Gifford RW Jr, Vidt DG. Blood pressure regulation in pheochromocytoma. Hypertension. 1982;4:193–9.

11. Prokocimer PG, Maze M, Hoffman BB. Role of the sympathetic nervous system in the maintenance of hypertension in rats harboring pheochromocytoma. J Pharmacol Exp Ther. 1987;241:870–4.

12.• Mancia G, Grassi G. The autonomic nervous system in hypertension. Circ Res. 2014;114:1804–14. https://doi.org/10.1161/CircresAHA.114.302524 **The paper highlights the major role of the parasympathetic and sympathetic autonomic dysfunction in the pathophysiology of essential hypertension.**

13. Imai Y, Abe MY, Nihei M, Sasaki S, et al. Hypertensive episodes and circadian fluctuations of blood pressure in patients with phaeochromocytoma: studies by long-term pressure monitoring based on a volume-oscillometric method. J Hypertens. 1988;6:9–15.

14. Grassi G, Seravalle G, Turri C, Mancia G. Sympathetic nerve traffic responses to surgical removal of pheochromocytoma. Hypertension. 1999;34:461–5. https://doi.org/10.1161/01.hyp.34.3461.

15. Landsberg L, editor. Catecholamines: physiology, pharmacology and pathology for students and clinicians. Philadelpelphia: Wolters Kluwer; 2017. p. 1–156.

16.•• Grassi G, Mark AL, Esler MD. The sympathetic nervous system alterations in human hypertension. Circ Res. 2015;116:976–90. https://doi.org/10.1161/CircResAHA116309261 **The review critically examines the methodological approaches employed to assess human sympathetic function in hypertension and the main results obtained so far.**

17. Tsujimoto G, Honda K, Hoffman B, Hashoimoto K. Desensitization of postjunctional α_1- and α_2-adrenergic receptor-mediated vasopressor responses in rat harboring pheochromocytoma. Circ Res. 1987;61:86–98. https://doi.org/10.1161/01.res.61.1.86.

18. Snavely MD, Mahan LC, O'Connor DT, Insel PA. Selective down-regulation of adrenergic receptor subtypes in tissues from rats with pheochromocytoma. Endocrinology. 1983;113:354–61. https://doi.org/10.1210/endo-113-1-354.

19. Higashi Y, Sasaki S, Nakagawa K, Kimura M, Sasaki S, Noma K, et al. Excess norepinephrine impairs both endothelium-dependent and independent vasodilation in patients with pheochromocytoma. Hypertension. 2002;39:513–8. https://doi.org/10.1161/hy02t2.102820.

20. Bruno RM, Ghiadoni L, Seravalle G, Dell'Oro R, Taddei S, Grassi G. Sympathetic regulation of vascular function in health and disease. Front Physiol. 2012;3:284. https://doi.org/10.3389/fphys.2012.00284.

21.• Virdis A, Savoia C, Grassi G, Lembo G, Vecchione C, Seravalle G, et al. Evaluation of microvascular structure in humans: a "state of the art" document of the working group on macrovascular and microvascular alterations of the Italian Society of Hypertension. J Hypertens. 2014;32:2120–9. https://doi.org/10.1097/HJH.0000000000000322 **The paper critically examines the main methodological approaches to assess human vascular function.**

22. Pacak K. Phaeochromocytoma: a catecholamine and oxidative stress disorder. Endocr Regul. 2011;45:65–90.

23. Grassi G, Seravalle G, Lanfranchi A, Cattaneo BM, Vailati S, Bolla GB, et al. Proc 7th European Meeting on Hypertension, Milan 1995: 73(abstract).