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Baroreflex sensitivity after kidney transplantation: arterial or neural improvement?

Pierre Boutouyrie[1,2,3], Luca Zanoli[4], Marie Briet[1,2,3], Alexandre Karras[1,2,3] and Michel Delahousse[5]

[1]Université Paris Descartes, Paris, France,
[2]Assistance Publique, Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Paris, France,
[3]INSERM U970, Paris, France,
[4]Department of Internal Medicine, University of Catania, Catania, Italy and
[5]Hôpital Foch, Paris, France

Correspondence and offprint requests to:
Pierre Boutouyrie;
E-mail: pierre.boutouyrie@egp.aphp.fr

The baroreflex adapts heart rate and peripheral resistances to acute and chronic changes in blood pressure. The baroreflex is a crucial function, especially for humans, which continually aims to adapt blood pressure to postural and behavioural changes by modulating the sympathetic/parasympathetic balance [1]. Baroreflex alteration has been reported in several clinical conditions such as ageing [2], hypertension [3], diabetes [4], chronic kidney disease [5] and heart failure [6]. In these conditions, baroreflex impairment has been related to pejorative outcomes [7].

Baroreflex is a very convenient word for summarizing very complex processes involving different sensor locations (carotid bulbs, aorta, lungs, atria, kidneys), large operating ranges (high pressure, low pressure) and various time constants (immediate, delayed) [8]. Studying the baroreflex is complex, but it always comes back to relating blood pressure changes to changes in heart rate. Various approaches have been developed including pharmacological modulation of blood pressure with infusions of vasodilating and vascoconstricting drugs and concomitant measurement of heart rate changes [1, 9] and mechanical stimulation of the baroreceptors with neck suction or with lower body negative pressure. More recently, methods based on spontaneous fluctuation of blood pressure and heart rate were developed to measure spontaneous baroreflex [10]. Baroreflex can be studied in the time domain by identifying series when variations in blood pressure and heart rate go in opposite directions (thereby obtaining the slope) [11] and in the frequency domain through spectral analysis of blood pressure and heart rate [9].

All of these classical methods for baroreflex assessment are limited by the fact that the signal sensed by baroreceptors is not the pressure by itself, but a stretch rate [12]. Thus, blood pressure has to be converted to stretch which represents the true signal received by the baroreceptors. The pressure/stretch relationship is the definition of arterial stiffness and stiffness of large arteries is a crucial component, known as the vascular component, of the baroreflex [13, 14]. Arterial stiffness determines the conversion of blood pressure into stretch of the baroreceptors embedded in the carotid wall via a transfer function ('TF' in Figure 1). Other TFs affect the way brachial or finger blood pressure is converted into central (carotid or aortic) blood pressure.

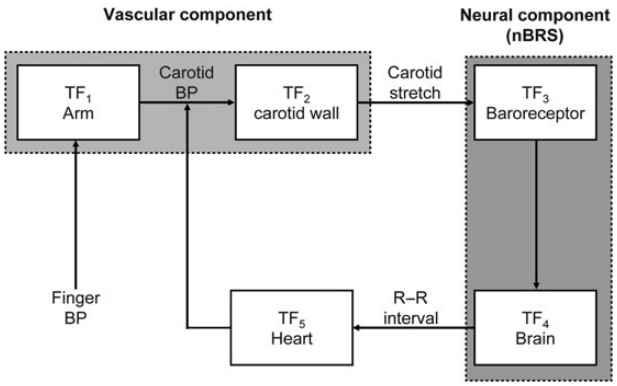

FIGURE 1: Representation of the vascular and neural components of the baroreflex (adapted from refs [7] and Saed *et al.* [15]). TF stands for transfer function, BP for blood pressure.

The neural components of the baroreflex cannot be addressed directly using the classical methods (Figure 1) [15]. Techniques have recently been introduced to study the neural components [16, 17]. These techniques involve the measurement of carotid bulb stretch along with heart rate and cross-spectral analysis.

End-stage renal disease is associated with high levels of morbidity and mortality, mostly due to cardiovascular disease. Chronic kidney disease-associated impairment of the baroreflex has been reported in the past and expresses a severe imbalance in the sympathetic/parasympathetic systems. Sympathetic tone is chronically increased (mainly because of unopposed stimulation of renal nerves by non-functioning kidneys [18]) and acutely stimulated (particularly by rapid variations of blood volume during the haemodialysis sessions). This high level of sympathetic stimulation is not sufficiently counteracted by the parasympathetic tone.

In the paper presented by Jayal *et al.* in the present issue of *NDT*, the authors report an increase in baroreflex sensitivity after kidney transplantation and state that this amelioration was related to an improvement in the augmentation index, an index of pressure wave reflection. This study was conducted in a limited number of patients ($n = 23$) but with very careful and detailed haemodynamic assessment using spontaneous baroreflex in the frequency domain, and classical pulse wave velocity and central blood pressure as vascular indexes. Results are appealing. Improvement of baroreflex sensitivity was clearly correlated with improvement in the augmentation index. However, interpreting the association of baroreflex sensitivity improvement with a decrease in the augmentation index is not evident. The augmentation index is considered by some authors as an index of arterial stiffness because increased stiffness makes the pressure wave return earlier during systole, thereby increasing wave reflections.

The augmentation index is also markedly dependent on peripheral resistance, which increases the intensity of wave reflection. The results of Jayal *et al.* regarding the relationship between improvement of baroreflex and augmentation index following transplantation can be interpreted as induced by chronic decrease in peripheral resistance and/or by improved arterial stiffness. The study might have been underpowered to detect the improvement in arterial stiffness (assessed through carotid to femoral pulse wave velocity), improvement which has been shown by others [19], and to relate changes in arterial stiffness with baroreflex sensitivity improvement. One of the qualities of the study is that measurements were available at 3 and 6 months after transplantation, but also just prior to it, which is quite unusual in transplantation studies. One of the limits of the study is that arterial stiffness was not measured at the site of the carotid bifurcations where the baroreceptors lie.

Transplantation is the most effective treatment of end-stage renal disease because glomerular filtration rate and most of the kidney endocrine functions are restored, but it is at the cost of a lifelong immunosuppression. Several questions remain regarding how transplantation can improve baroreflex and its relationship to arterial properties, especially for the role of chronic vasoconstriction and sympathetic tone which are the more likely explanations for an altered augmentation index. To what extent do transplanted kidneys re-innervate in human transplantation? Re-innervation has been demonstrated for transplanted hearts [20] so there is no reason why kidneys should not do the same [21]. What is the role of failing native kidneys and what would have been the results if failing kidneys were removed or denervated? Native kidneys are a very strong cause for increased sympathetic activity [18], and transplantation does not correct increased sympathetic activity until the failing kidneys are removed [22]. In the present study, since failing kidneys were kept *in situ*, the improvement of baroreflex function can only be explained by improved arterial properties or improved neural components. Unfortunately, the method used in the study by Jayal *et al.* did not enable neural and vascular components of the baroreflex to be examined, therefore the relative contribution of improved (if any) arterial properties or improved neural components cannot be disentangled. We do not yet know what the relative contributions of restoring glomerular filtration rate or restoring endocrine function on improvement of arterial and baroreflex sensitivity alterations are. By studying carotid properties and the neural components of baroreflex sensitivity in greater depth, future studies may be able to answer these important questions.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Kaur *et al.* Renal transplantation normalizes baroreflex sensitivity through improvement in central arterial stiffness. *Nephrol Dial Transplant* 2013; 28: 2645–2655.)

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