Mechanisms of Experimental and Human Renovascular Hypertension

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Introduction

Goldblatt and his colleagues published their pioneering work on experimental renovascular hypertension in 1934 [58]. They demonstrated that the reduction of renal perfusion pressure, induced by placing a clamp around one renal artery in dogs, produced sustained hypertension. Since this classic experiment, thousands of studies have been done to evaluate the mechanisms involved in the development and maintenance of renovascular hypertension. There are three different ways of increasing blood pressure by narrowing the renal artery with a clamp. Two-kidney- one-clip (2K-1C) hypertension is induced by decreasing renal perfusion pressure in one kidney and leaving the contralateral kidney untouched. In one-kidney, one-clip hypertension, the opposite kidney is removed. Finally, two-kidney, two-clip hypertension is produced when renal perfusion pressure is reduced in both kidneys. The evaluation of the mechanisms responsible for the maintenance of high blood pressure during the acute and chronic phases of hypertension in these experimental models is very important since it is accepted that the same pressor mechanisms are involved in the maintenance of high blood pressure in human renovascular hypertension.

This chapter will review current knowledge regarding the relative role of the different mechanisms that seem to be involved in both the increase of blood pressure after the induction of 2K-1C hypertension and the maintenance of high blood pressure during the acute and chronic phases of renovascular hypertension. Changes after surgical correction of hypertension will be also evaluated.

Induction of Renovascular Hypertension: Methodology

The induction of 2K-1C hypertension is performed by placing solid silver clips of varying internal diameter (ID) around one renal artery, the opposite renal artery remaining intact. Fig. 1 illustrates changes in arterial pressure over 16 weeks after induction of hypertension in rats with a clip of 0.20-mm ID [135]. Arterial pressure increased gradually over 10 weeks, and later a slight decrease was found in the hypertensive rats. The increase in blood pressure was significant in 75% of the animals at 1–2 days, while it was necessary to wait for some days in certain rats until the development of hypertension. A similar pattern of increment in blood pressure has been reported previously by Swales et al. [150] and De Forest et al. [27]. However, the level of arterial pressure obtained after induction of hypertension varies between different
groups [11, 27, 135]. The increment of blood pressure after placement of a renal arterial clip depends on its internal diameter, the methodology employed (clip proximal or distal to aorta), body weight, type of clips used, and the level of sodium and potassium intake or the sodium/potassium ratio in the diet. Leenen and De Jong [88] demonstrated in rats that systolic blood pressure increased from 120 to 140 mmHg 21 days after renal perfusion pressure decreases in one kidney, by placing a clip with 0.35-mm ID. On the other hand, when a clip with 0.20-mm ID was used, systolic blood pressure increased to 215 mmHg. Smith and Bishop [147] correlated the weights of ischemic/contralateral kidneys with blood pressure in 2K-1C hypertensive rats and identified a range of ischemic/contralateral kidneys that would exclude the animals least likely to become hypertensive. Six to eight weeks after clipping, 100% of the animals with an ischemic/contralateral ratio of 0.5–0.8 had a blood pressure greater than 150 mmHg. Less than 50% with an ischemic/contralateral ratio below 0.4 or above 0.9 were hypertensive. They suggested that ischemic/contralateral kidney ratios provide an objective way to compare treatment groups and to evaluate whether a given 2K-1C animal would have become hypertensive.

In one-kidney, one-clip hypertension, the contralateral kidney is removed either previously (in a separate surgical session) or at the time of renal artery stenosis. More severe hypertension is induced when nephrectomy of the contralateral kidney is done 4 weeks before renal artery narrowing [89]. It is currently accepted that blood pressure increases more rapidly in the one-kidney than in the two-kidney, one-clip hypertension. Severe hypertension is produced after 21 days of decreasing renal perfusion pressure with a clip 0.30-mm ID. To obtain a similar increment of blood pressure in the 2K-1C model, stenosis of the renal artery should be done with a clip of 0.20-mm ID [89]. However, other investigators have reported similar levels of hypertension in the two models [11, 150]. There are no obvious explanations for the different pattern of increasing blood pressure in these experimental models of hypertension.