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COMMENTARY

Vascular hyper-reactivity following arterial balloon injury: distant and delayed effects

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The adverse functional effects of balloon angioplasty include simple procedure failure, compromise of vessel lumen (rupture), and restenosis. A much less well-defined repercussion of balloon injury to arteries is a paradoxical alteration in vascular reactivity at an anatomically distant site. The paper by Accorsi-Mendonça in the current issue presents new data showing that, following balloon injury to the rat left common carotid artery, there is a delayed hyperreactivity to both phenylephrine and angiotensin II in the contralateral artery. The pharmacological basis of these effects is unknown, although the authors demonstrate that products of cyclooxygenase (COX) 1 or 2 are responsible for the hyperreactivity to angiotensin II and phenylephrine, respectively. The absence of delayed hyperreactivity to these agents in the aorta of injured rats would suggest that a humoral factor is not involved.
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Balloon angioplasty is a common intervention for the treatment of blood vessel stenoses, particularly of the coronary vasculature. The procedure involves passing a small balloon over the region of occlusion, such as an atheromatous plaque, and inflating it to compress the blockage and restore blood flow (Grech, 2003). It is a remarkably effective technique, although its success is somewhat marred by the subsequent rates of restenosis. The inflation of the balloon represents a physical insult to the blood vessel, and there is growing evidence that this injury may have significant physiological repercussions itself, irrespective of reocclusion. The balloon directly inflicts significant trauma to the vascular endothelium, which is evidenced by an immediate loss of endothelial-dependent relaxation, and is itself associated with a concomitant induction of smooth muscle cell proliferation and neo-intima formation (Schwartz & Henry, 2002). Interestingly, there is also less well-known evidence that balloon injury can induce physiological changes at sites anatomically distant from, as well as at the site of injury itself.

It has been previously shown that 24 h after balloon injury to the rat left common carotid artery, there was a marked decrease in the density of protein gene product 9.5-, substance P- and calcitonin gene-related peptide-containing neurons innervating the artery. Most surprisingly, however, was the finding that there was a substantial increase in the density of these neurons innervating the artery contralateral to injury (Milner *et al*., 1997). At 28 days, the innervation of both arteries had returned to control levels. Bruijns *et al.* (1998) showed that in chemically sympathectomised rats, a 2-week exposure to angiotensin II (Ang II) following balloon injury resulted in increased smooth muscle cells DNA synthesis, but only on the contralateral side. Thus, angioplasty may also cause perivascular damage, which induces changes in the density of nerves supplying both the ipsi- and contralateral vessels, and would appear to play an important role in mediating at least some of the distant effects of balloon injury.

In the current issue of the journal, Accorsi-Mendonça *et al.* (2004) present intriguing evidence showing that following balloon injury, there is a delayed hyper-reactivity to both phenylephrine (PE) and Ang II in contralateral rat carotid arteries, occurring between 4–7 and 15–30 days, respectively, thereafter returning to control levels. Although not directly shown in this study, part of the reason for the delayed onset of these effects may be related to known changes in α_1-adrenoceptor expression immediately following injury, and the mechanistic interaction between these receptors and Ang II (Bruijns *et al*., 1998). The authors show that denudation of the endothelium augments the response to phenylephrine in control arteries, consistent with the expected loss of endothelium-derived relaxing factors. However, in contralateral arteries, removal of the endothelium had no effect on the maximal efficacy of PE at 4–7 days postinjury, which was suggested to be due to a reduction in the release of endothelium-derived factors, although the absence of changes in resting membrane potential, resting blood flow, and potency/efficacy of the endothelium-dependent vasodilator, bradykinin, do not fully support this conclusion.

An alternative explanation would be that there was a simultaneous increase in nonendothelium-derived relaxing factors, possibly NO, as well as the release of an endothelium-derived constricting factor. These together would account for both the comparative hyporeactivity to PE without the endothelium and the hyper-reactivity to PE with it. Indeed, the experiments performed using a selective inhibitor of cyclooxygenase 2 (COX-2), suggest that the hyper-reactivity to PE is due to the release of a constricting prostanoid, which may or may not be endothelium-derived. These observations are

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supported by Furuhashi *et al*. (2000), who showed that vasoconstriction induced by norepinephrine in rat carotid arteries is also modulated by constricting prostanoids derived from both the endothelium and vascular smooth muscle.

In the case of Ang II, it appears that the hyper-reactivity observed between days 15 and 30 is also due to a constricting prostanoid, although it appears to be largely the product of the COX-1 isoform, based on its sensitivity to valeryl salicylate. Moreover, this prostanoid is likely to be part of the normal physiological response to Ang II since it occurs in both control and contralateral arteries. Like PE, the contralateral hyper-reactivity to Ang II is largely unaffected by the endothelium, although the maximal effect achieved is similar to control arteries suggesting that the location of the COX-1 is primarily the endothelium. The reasons for this apparent isoform specificity is unclear, although certainly intriguing. While it is known that both isoforms are expressed in the neo-intimal layer following direct injury (ipsilateral side) (Connolly *et al*., 2002), there is a distinct lack of data regarding expression on the contralateral side, or indeed why COX-2 is being expressed at all, particularly as it is not thought to play a role in intimal hyperplasia anyway.

There is convincing evidence that balloon injury causes vascular effects far away from the site of injury. Sympathetic innervation plays some role in the regulating vascular reactivity, although the new data provided by Accorsi-Mendonça also suggest that changes in COX expression/activity within the endothelium and/or smooth muscle of the contralateral vessel are also important, although clearly, these are still early findings. These data pose some interesting questions with regard to the potential systemic adverse effects of angioplasty and the pathophysiological significance of these pathways in humans awaits more detailed investigation.

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