Is there life after plaque rupture?

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Abstract
Little is known of the relationship between plaque rupture and adaptive geometric remodelling, especially in the context of unstable atherosclerosis. We have assessed remodelling in the proximal brachiocephalic arteries of fat-fed apoE (apolipoprotein E)-knockout mouse. The rate of vessel expansive remodelling is similar in vessels with plaques and without plaques, suggesting that the presence of plaque is not necessary for remodelling to occur. In vessels with plaques, the degree of expansive remodelling was strongly associated with the stability of the plaque. Vessels with stable plaques (i.e. with neither buried fibrous caps nor acute plaque ruptures) showed no expansion, whereas those with evidence of plaque rupture expanded at a significant rate. Vessels with stable plaques suffered significant loss of lumen over time, but those with unstable plaques maintained lumen area over time. Pravastatin treatment of male apoE-knockout mice caused a 5-fold increase in fibrous cap thickness and, although it did not influence overall rates of vessel remodelling, it significantly increased both the amount of vessel expansion and the period of time between plaque ruptures, suggesting that it increases the ability of the plaque to resist the rupturing force caused by vessel expansion. These results suggest that vessel expansion in brachiocephalic arteries of fat-fed apoE-knockout mouse does not require the presence of plaque. When a plaque is present, the outward remodelling force is exerted across its cap: vessels with smaller outward remodelling forces cannot overcome the strength of the cap, and the plaque remains stable. When the remodelling force is greater than the strength of the cap, the plaque ruptures. Thus plaque rupture can be viewed as a consequence of vessel remodelling. Interventions that strengthen the plaque, such as pravastatin therapy, do not alter remodelling parameters but instead allow for more outward remodelling before a rupture is caused.

It is intriguing to note that, although most acute coronary events are caused by atherosclerotic plaque rupture [1], most plaque ruptures do not result in any symptoms [2]. In other words, although plaque rupture can be catastrophic, it usually is not. Why should this be? One possibility is that the ruptured plaque can heal, and the increased bulk of the lesion can be accommodated by remodelling of the vessel.

Arteries that harbour atherosclerotic lesions are known to have altered physical dimensions, which may preserve, either fully or partially, luminal cross-sectional area despite the obstructive bulk of the lesion. This means that blood supply is maintained at a relatively normal rate for longer than would otherwise be the case. In some situations, the opposite may happen and the artery may shrink, further compromising the lumen [3]. This expansive or constrictive remodelling is clearly an important determinant of the impact of lesion formation on the perfusion of distal organs with blood, and thus of atherosclerosis on health.

Because correlational studies that compare total vessel cross-sectional area with plaque size in human coronary arteries show a reasonably close linear relationship [4], it is usually assumed that some kind of homoeostatic mechanism is at work and that plaque growth can drive vessel expansion. However, causation has not been proved. Furthermore, plaque rupture might disrupt any homoeostatic equilibrium because the effective luminal cross-sectional area could be suddenly altered by an accompanying mural thrombosis. Studying the influence of plaque rupture on vessel remodelling is difficult in humans, because the location and timing of the rupture cannot be predicted with certainty. Comparative analysis of vessel dimensions in patients with stable or unstable angina suggests that unstable coronary syndromes are associated with a greater degree of positive remodelling [5,6], but it is impossible to differentiate between the possibility that coronary thrombosis causes the remodelling response and the possibility that positively remodelled vessels are more prone to thrombosis. Also, the vessel segment under study is different in each patient, which introduces an additional element of uncertainty into the analysis.

We have developed a mouse model of atherosclerotic plaque rupture that involves feeding a high-fat diet (21 % lard and 0.15 % cholesterol) to apoE (apolipoprotein E) homozygous knockout mice, with ruptures developing in the brachiocephalic arteries [7–9]. The unstable plaques carry on developing over many months of high-fat feeding, with ruptures occurring at approx. 1–2 months. Plaque ruptures are defined for our purposes as either acute (a visible breach in the fibrous cap with accompanying haemorrhage into the core) or as previously occurring and now healed (one
or more fibrous caps buried in the plaque) [10]. Ruptures occur in the proximal 150 \( \mu \)m of the vessel, so we have tight anatomical localization of the phenomenon, which makes comparison of results across studies straightforward.

We have taken advantage of a large archive of historical murine morphometric data, obtained with this model, to investigate arterial remodelling in the context of plaque instability. In total, 446 apoE-knockout mice, fed high-fat diet for up to 1 year, and all perfusion exsanguinated and then formalin fixed at arterial pressure \textit{in situ}, have been combined into one database. Taking all of these animals together, there is a strong and significant positive linear correlation between plaque area and vessel area \((r^2 = 0.52; P < 0.0001)\). Since plaques grow with time, it would be expected that vessels also expansively remodel with time, which is indeed the case. Vessel area increases at the rate of \(+ 4.0 \pm 0.3 \times 10^3 \mu \text{m}^2/\text{week} \) \((P < 0.0001)\). This is not simply a reflection of growth and maturation because fat-fed strain-matched wild-type mice, which do not develop atherosclerosis, showed no expansion of this same vessel over the course of a year \((+ 0.2 \pm 0.6 \times 10^3 \mu \text{m}^2/\text{week}; P = 0.75)\). However, it is not true to say that all vessels with plaques expansively remodel: in vessels with stable plaques the vessel area did not change \(+ 0.1 \pm 1.4 \times 10^3 \mu \text{m}^2/\text{week}; P = 0.95\), but in vessels with unstable plaques there was a significant increase in vessel area of \(3.4 \pm 0.4 \times 10^3 \mu \text{m}^2/\text{week} \) \((P < 0.0001)\). These two rates of vessel expansion are significantly different \((P = 0.034)\), despite the fact that the rates of plaque expansion are not significantly different \((+ 2.2 \pm 0.7\) and \(+ 3.4 \pm 0.2 \times 10^3 \mu \text{m}^2/\text{week} \) respectively; \(P = 0.23)\). There was no significant influence of gender on vessel expansion: males and females showed similar rates for both stable plaques \((P = 0.16\) for the comparison) and unstable plaques \((P = 0.78\) for the comparison). These results suggest that plaque growth does not in itself cause an increase in the underlying rate of vessel expansion at this site, which supports the finding that there is appreciable vessel expansion even in the absence of plaque.

Since stable atherosclerotic plaques grow but the vessels that harbour them do not expand, loss of lumen would be expected to occur. Indeed, in vessels with stable plaques, there is a significant reduction in lumen area at a rate of \(- 2.4 \pm 1.1 \times 10^3 \mu \text{m}^2/\text{week} \) \((P = 0.034)\) and this is significantly different from the situation in unstable plaques \((P = 0.014)\), where no significant change in lumen area is observed \((+ 0.2 \pm 0.2 \times 10^3 \mu \text{m}^2/\text{week}; P = 0.362)\).

Our results suggest that there is an association between stable plaques and lack of remodelling on the one hand, and between unstable plaques and expansive remodelling on the other. This could mean either that stable plaques prevent vessel expansion or that vessel expansion causes plaque rupture. Results from animals treated with pravastatin suggest that the latter hypothesis is more likely to be true. Brachiocephalic artery plaques in mice receiving pravastatin have significantly thicker fibrous caps and a significantly lower lipid content [9], both of which are likely to increase plaque strength. Indeed, treated animals had significantly fewer plaque ruptures at this site. However, there was no change in any parameter of expansive remodelling in these plaques, suggesting that increasing plaque stability does not restrict vessel remodelling. The results are consistent with the idea that expansive forces cause plaque rupture when they overwhelm the strength of the plaque: stronger plaques can resist the expansive force for longer and thus rupture less frequently. Supporting this, in control animals the mean time between ruptures was \(12.3 \pm 0.5\) weeks, but in animals treated with pravastatin this was increased by \(73\%\) to \(21.3 \pm 1.5\) weeks \((P < 0.0001)\).

These results lead to the rather challenging hypothesis that vessel expansion and plaque rupture are linked phenomena and that there is an expansive force generated within the brachiocephalic artery that exerts tension across the fibrous cap. For as long as the strength of the cap is sufficient to withstand this tension, the plaque remains stable; however, if the tension becomes too great for the cap it breaks, precipitating a plaque rupture. In vessels with stable plaques, expansive remodelling is not seen. One possible explanation for this would be that the plaque itself, and particularly the fibrous cap, is functioning as an internal brace or strut across the lumen, physically restricting vessel expansion. However, results from pravastatin-treated animals lead us to reject this idea. In these animals, fibrous cap thickness was increased 5-fold and plaque lipid content was significantly reduced. If a strong fibrous cap can withstand a greater tensile force, pravastatin treatment would be expected to be associated with a reduction in the rate of vessel expansion. However, there were no changes in any remodelling parameters in pravastatin-treated animals.

An alternative explanation for the lack of vessel remodelling when a stable plaque is present is that these represent vessels with smaller expansive forces. According to this notion, the small force is insufficient to break the cap so the plaque is stable, and it is also insufficient to enlarge the vessel over time. Ruptured plaques would represent the situation where there is adequate expansive force, breaking the cap and driving vessel enlargement. A treatment such as pravastatin that strengthens the cap would be predicted to have no effect on vessel remodelling but to reduce the incidence of plaque rupture, which is what is observed. The amount of vessel expansion that occurs between plaque ruptures is \(221 \pm 7 \mu \text{m}^2\) in control animals but is increased by \(24\%\) to \(274 \pm 14 \mu \text{m}^2\) in pravastatin-treated mice \((P = 0.0005)\); in control animals, the mean time between ruptures was \(12.3 \pm 0.5\) weeks, but in animals treated with pravastatin this was increased by \(73\%\) to \(21.3 \pm 1.5\) weeks \((P < 0.0001)\). We therefore conclude that plaque rupture is a passive consequence of vessel expansive remodelling.

A further speculation prompted by the suggestion that vessel expansion can cause plaques to rupture is that arteries that are completely surrounded by muscular tissue might be expected to be less vulnerable to rupture, because the muscle would tend to resist the outward excursion of the vessel wall, buffering the tensile force generated across the fibrous cap. Human left anterior descending coronary arteries run epicardially and then enter the myocardium approximately one-third of the way along their length. Plaque ruptures
are very much more frequent in the epicardial region of this artery than in the intramyocardial region [11,12], supporting the idea that vessel expansion leads to plaque rupture. Murine coronary arteries are intramyocardial for their entire length, and we have not observed plaque ruptures in these vessels. Instead, we often see obliterative atherosclerotic lesions that completely fill the lumen [8]. Similar lesions have been shown by others [13,14]. When vessel expansion is circumscribed, lumen is lost.

To summarize, we suggest that expansive geometric remodelling is a cause of plaque rupture in the brachiocephalic arteries of fat-fed apoE-knockout mice. Vessel expansion occurs even when no plaque is present, but arteries with stable plaques show no such expansive remodelling. These results suggest that the fibrous caps of plaques are put under tension by vessel expansion; when the expansive force becomes too great, the cap fails and rupture occurs. This may be an adaptation, because it has the beneficial effect of allowing the lumen area to be restored and maintained, and this could explain the puzzling fact that plaque rupture is usually asymptomatic. Processes within the plaque that reduce its strength predispose to rupture because the degree of tension required to break the cap is reduced. On the other hand, treatment with a statin, which increases fibrous cap thickness and reduces plaque lipid content, increases the ability of the plaque to resist the rupturing force caused by vessel expansion and thus increases the time interval between ruptures.

References

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