Editorial Comment

Age as a Modulator of Coronary Capillary Angiogenesis

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A half century ago Roberts and Wearn\(^1\) published their classical study on human hearts, which demonstrated that 1) capillaries multiply during postnatal growth to compensate for the increase in muscle fiber size, 2) muscle-to-capillary ratio attains a value of approximately 1:1 at maturity, and 3) this ratio persists throughout life. They also found that hypertrophied hearts of adults consistently had lower capillary densities than hearts that were not hypertrophied. Since that time, the prevailing view has been that cardiac hypertrophy in humans is accompanied by little or no capillary growth. However, the article by Rakusan and colleagues\(^2\) that appears in this issue of *Circulation* is the first to systematically document capillary parameters with regard to postnatal growth and pressure-overload hypertrophy in humans. There are several important new findings in this paper that provide insights into coronary angiogenesis.

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One important finding in this study is that the data concerning vascular growth in human hearts are generally consistent with those obtained from experimental animals. The data on human hearts\(^3\) indicate that although capillary growth does not keep pace with the increase in mass of the heart during the transition from infancy to childhood to adulthood, capillary angiogenesis is not arrested. Thus, a fourfold increase in heart mass from infancy to childhood is associated with only a 27% decrement in capillary density. Similarly, capillary density in rats declines only 23% between 4 and 10 weeks (weaning and puberty, respectively), whereas left ventricular (LV) weight increases 2.6-fold.\(^3\) Moreover, the relation between capillary domains and heart mass during postnatal growth is quite similar in the two species.\(^2,^4\) More recently, Smolich and colleagues\(^5\) have documented a rather marked capillary angiogenesis in sheep during postnatal growth. Their data show a decrease in myocyte-capillary ratio from birth to adulthood, a period characterized by nearly a fourfold increase in myocyte cross-sectional area.

Data from the human hearts analyzed by Rakusan et al\(^2\) indicate that the timing of LV pressure overload determines the extent of capillary growth; i.e., capillary proliferation keeps pace with the increase in mass when aortic stenosis is congenital but not when it is acquired. This finding, coupled with the data on normal hearts from infants, children, and adults, provides support for the hypothesis that coronary angiogenesis is age dependent. This hypothesis is supported by studies using models of so-called “physiological hypertrophy.” Most studies on exercise-induced capillary growth indicate that the best response occurs in young animals.\(^6-^9\) Exercise has been shown to normalize capillarity in hearts of spontaneously hypertensive rats when initiated before puberty\(^10\) but not when initiated in adults.\(^11\) Capillary density in hearts of thyroxine-treated rats is elevated by a greater magnitude when the treatment begins before puberty.\(^12\)

However, the capacity for coronary angiogenesis is not lost in adults and appears to persist even into old age. Support for this conclusion comes from data on rats with long-term genetic\(^13,^14\) or renal\(^15,^16\) hypertension, from dogs with long-term renal hypertension,\(^15,^16\) and from pigs\(^17,^18\) and rats\(^18\) with thyroxine-induced cardiac hypertrophy. A report on human hearts also suggested that capillary proliferation occurred when a heart reached a critical weight.\(^19\) Accordingly, the inadequate vascular growth commonly observed in many models of hypertrophy is a dilemma and suggests that the mechanisms governing angiogenesis are operable only under certain conditions. Hypertension per se does not appear to play a role in the capillary response in models of pressure overload, because the work of Rakusan et al\(^2\) clearly shows that capillary growth is similar in the presence and absence of coronary hypertension, as seen by comparisons between hypertrophic hearts from patients with congenital coarctation of the aorta and aortic valve stenosis. This finding is consistent with those from experimental animals indicating that ventricular mass rather than coronary pressure is the main determinant of capillary density.\(^20\)

In addition to capillary numerical density, the traditional measure of capillarity, there are some other indices of growth that are not suitable for evaluation when hearts are obtained at necropsy. Recent work indicates that volume density and minimal intercapillary distance (mean distance between the edges of two adjacent capillaries) are unaltered in senescent beagles despite an 18% decrease in numerical density between 1 and 11 years of age.\(^21\) Vascular remodeling, resulting in an increased mean lumen diameter, compensated for the decrement in numerical density associated with an increased heart mass over the life span.

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In view of these findings, it is apparent that capillary neoformation occurs in adults under the appropriate conditions even when pressure overload is the growth stimulus. A major obstacle to understanding coronary vascular growth is that the mechanisms of angiogenesis are not well understood. Angiogenesis is a complex process involving a cascade of events that include mechanical factors, cell-to-cell interactions, extracellular matrix molecules, and growth factors. Because growth factors are found in nonproliferating tissues, the fundamental questions concern inhibition and stimulation of endothelial growth factors. From the numerous studies relating to cardiac hypertrophy in adults, it is clear that the appropriate stimulus is absent or limited under certain circumstances but not others. For example, capillary density declines and minimal coronary vascular resistance rises markedly during the first 6 weeks of renal hypertension in dogs despite a relatively modest (27%) increase in LV mass. In contrast, by month 7, when hypertrophy has increased to 47%, minimal coronary vascular resistance and arteriolar density are normal, and considerable capillary growth has occurred. This suggests that the stimulus for angiogenesis in this circumstance became effective only after a period of time or a critical level of hypertrophy.

Although growth factors are ultimately involved in angiogenesis, establishing the physiological basis for the mobilization of such molecules is an important undertaking. At the present time, there is good support for the hypothesis that mechanical factors (e.g., wall tension or stretch) initiate the events that lead to angiogenesis in the heart. Future studies are faced with the challenge of discovering the events that stimulate and regulate coronary vascular growth. Such advances would form the basis for possible interventions that would improve oxygen delivery to the cardiac myocyte.

References

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