Coronary Plaque Neovascularization and Hemorrhage
A Potential Target for Plaque Stabilization?

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Angiogenesis, or the growth of new blood vessels from existing host vessels, is increasingly being recognized as important in the growth and progression of atherosclerosis, the primary cause of coronary artery and cerebrovascular disease. Neovascularization of atherosclerotic plaques was first noted by Koester (1) in 1876. Later Barger et al. (2) proposed that the growth and extension of adventitial blood vessels called vasa vasorum (VV) into the intima occurs as a response to tissue hypoxia, which occurs when the intima thickens beyond the diffusion limits of oxygen and nutrients (approximately 350 μM) (3). Indeed, increases in hypoxia-inducible factor alpha, a transcription factor that is up-regulated under hypoxic conditions and promotes hypoxia-dependent neovascularization, have been found in human atherosclerotic plaques (4).

Because many of the VV that grow into the plaque are immature (i.e., they lack mural cells and competent endothelial cell [EC] junctions), they are inherently leaky, permitting inflammatory cell infiltration and influx of blood constituents, especially erythrocytes, into the plaque. Most of the intraplaque vessels are endothelialized, but only a few possess mural pericytes and smooth muscle cells (5,6). The lack of mural cells and poorly formed EC junctions contribute to the incompetence of immature intraplaque VV. Erythrocyte membranes, rich in phospholipids and free cholesterol, and free hemoglobin, a source of oxidative damage and reactive oxygen species, contribute significantly to necrotic core expansion and inflammatory cell infiltration, 2 features essential to all high-risk plaques (7).

Neovessels also promote the entry of leukocytes into the plaque by up-regulation of adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin (8). Increased matrix metalloproteinase release from activated macrophages and proteases secreted from mast cells cause further damage to microvessels and facilitate intraplaque hemorrhage (9).

In this issue of JACC, work by Gössl et al. (10) lends further support to the concept that coronary VV neovascularization plays an important role in plaque progression through promotion of intraplaque hemorrhage. Using hearts from 15 patients obtained by autopsy, they demonstrated that VV density was higher in nonstenotic (defined as ≤50% lumen diameter stenosis) and noncalcified plaques compared with normal segments. As expected, the amount of iron and glycophorin A (an anion-exchange protein specific to erythrocytes) was significantly higher in nonstenotic and stenotic plaques compared with normal segments. As expected, the amount of iron and glycophorin A (an anion-exchange protein specific to erythrocytes) was significantly higher in nonstenotic and stenotic plaques compared with normal segments.

Perhaps more novel and interesting is their finding that in calcified stenotic plaques, VV spatial density was lowest; however, relatively high amounts of glycophorin A and iron were found in these lesions, suggesting that intraplaque hemorrhage is associated with plaque calcification.

These findings confirm earlier work linking hemorrhage to coronary plaque progression. In a relatively large number of human coronary plaques from victims

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Editorial Comment

Finn and Jain

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tation of VV density histologically has also been
shown to correlate with plaque progression and rein-
forces the authors’ conclusions (12).

The association of intraplaque hemorrhage with
plaque calcification is a more novel aspect of this
study. Although coronary artery calcification correlates
with the severity and extent of coronary disease at
autopsy (13), there does not appear to be a linear
relationship between coronary calcium and risk for
future coronary events (14). Pathologically, ruptured
plaques do demonstrate significantly higher calcium
levels than do thin cap fibroatheromas (i.e., vulnerable
plaques), but the causes for this remain unknown (15).
This same relationship holds true for mean number of
VV and for hemosiderin-laden macrophages (another
sign of previous hemorrhage) (12); therefore, it is
tempting to speculate that increases in coronary cal-
cium levels seen in ruptured plaque may result from
hemorrhage. However, neither study demonstrates a
cause and effect phenomenon, which is essential to
furthering our understanding of the relationship of
coronary calcification and plaque stabilization. In-
stead, it begs the question of how and why heavy
calcification occurs in human coronary atheroscle-
rotic disease and whether it is simply a healing response to
hemorrhage.

Although not specifically addressed in this study,
another important and related question involves un-
derstanding how and why hemorrhage occurs in
human coronary atherosclerotic lesions. Recently,
Sluimer et al. (6) demonstrated abnormalities such
as incomplete endothelial junctions and basement
membrane detachment in human intraplaque ECs.
In addition, there was monocyte and mast cell
accumulation in these areas, substantiating the con-
cept that intraplaque microvessels are abnormal and
thus provide entry points for erythrocyte and other
blood cell components into the plaque. However,
no change in mural cell coverage was observed from
early, advanced, and ruptured coronary plaques,
suggesting lack of mural cell coverage alone may not
be responsible for intraplaque hemorrhage. This
paradigm, that pathologic angiogenesis within plaques
leads to hemorrhage, would be strengthened by in vivo imaging data.

Further work needs to be done to understand
precisely how and which molecules regulate the key
pro-angiogenic and antiangiogenic factors in the VV
within the plaques that show hemorrhage. The mecha-
isms responsible for the abnormal EC morphology
seen in intraplaque vessels undoubtedly involve vas-
cular endothelial growth factor (VEGF). Angiogenesis
depends on EC invasion and proliferation as well as
pericyte coverage of vascular sprouts, processes that are
coordinated by VEGF and platelet-derived growth
factor (PDGF) (16). VEGF disrupts EC junctions
and disrupts vascular smooth muscle cell function by
inhibiting PDGF-induced pericyte coverage of nas-
cent vascular sprouts (17,18). Placental-like growth
factor (PIGF) also stimulates vascular permeability,
and its expression has been associated with plaque
vulnerability (19). The Tie receptors, Tie1 and Tie2,
and 2 ligands for Tie2, Ang1 and Ang2, are also
critical for vessel formation and maturation. Sources of
Ang1 and Ang2 are mural cells and ECs, respectively.
Ang1 is known to stabilize nascent vessels and make
them leak resistant, presumably by facilitating com-
munication between ECs and mural cells. However,
the mechanism of vessel maturation by Ang1 is far
from clear. The role of Ang2 appears to be contextual.
In the absence of VEGF, Ang2 acts as an antagonist
of Ang1 and destabilizes vessels, ultimately leading to
vessel regression. In the presence of VEGF, Ang2
facilitates vascular sprouting. A high Ang2/Ang1 ratio
has been found in vulnerable neovascularized plaques
(20). Other molecules and growth factors have also
been shown to play a role in vessel maturation.

Another avenue of interest raised by the present
study is whether or not it might be possible to prevent,
destroy, or “normalize” neovessels within plaques.
This topic has many parallels in other fields of
medicine, especially oncology. Given the dependence
of tumor growth and metastasis on blood vessels,
inhibition of new vessel formation or destruction of
existing vessels of tumors has been one of the most
exciting areas of cancer research for the past decade.
Most of the clinical trials to date have tested agents
that neutralize VEGF or inhibit its signaling.
We have recently proposed—and demonstrated both pre-clinically and clinically—that antiangiogenic agents can prune and “normalize” the abnormal vasculature of tumors (Fig. 1) (21). Based on similarities to the structure and function of tumor vessels, could the judicious application of antiangiogenic agents prune and normalize immature intraplaque VV, thereby preventing intraplaque hemorrhage (22)?

The successes of anti-VEGF strategies in cancer biology raise the intriguing question of whether such therapy may be applicable to atherosclerosis. However, this strategy may hold more potential pitfalls than promises given the increased risks of atherothrombotic events seen with systemic antiangiogenic therapies and the reliance of coronary collateral formation on similar angiogenic pathways. Newer agents that might normalize abnormal vasculature without affecting healthy vessels such as anti-PIGF antibodies are currently being developed and may be a more tenable strategy (23,24).

In conclusion, the work of Gössl et al. (10) lends further insights into the association of neovascularization and hemorrhage with coronary atherosclerosis. Further work needs to be done to understand the causal relationship between hemorrhage and plaque calcification. Until the regulatory molecular mechanisms of intraplaque microvessel formation are better understood, we cannot be sure that the 2 are related or just coincidental bystanders. These and other recent data suggest that strategies to “normalize” intraplaque neovessels to prevent hemorrhage may be promising new avenues for the prevention of coronary events.

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