News Release

Title

Dynamics of angiogenesis in ischemic areas of the infarcted heart

Key Points

- New vessels are developed from the endocardium of left ventricle in mammalian heart.
  ------ Coronary circulation has been believed to be the unique system of heart perfusion.
- A part of cardiomyocytes was oxygenized by the new vessels developed from left ventricle.
  ------ The therapy to enhance angiogenesis from left ventricle could rescue more cardiomyocutes.
- Our data showed that the specific area along endocardium is a useful target for future therapies besides ischemic border area.
  ------ The same phenomenon was found in the human samples by the pathological examination.

Summary

A group of researchers in Department of Cardiology, Nagoya University Graduate School of Medicine and Kobe University Graduate School of Medicine reported that new vessels directly develop from left ventricle through endocardium after myocardial infarction and perfuse ischemic area, and newly formed vessels are not connected to coronary circulation which is believed to be unique system of heart perfusion.

Reperfusion therapy of occluded coronary vessels by catheter intervention decreases infarction area and can improve patient prognosis in myocardial infarction. However, a subset of patients requires ventricular assistance devices or heart transplantations, because of the extreme impairment of cardiac function. New treatments that use angiogenic or anti-apoptotic factors, and cell-based therapies are expected to alleviate heart damage. But clinical trials involving vascular endothelial growth factor (VEGF) or fibroblast growth factor (FGF) have not yielded the expected results; thus, no effective or innovative therapies have been developed for MI

Here, we describe a novel circulatory system wherein new vessels develop from the endocardium of the left ventricle to perfuse the hypoxic area and salvage damaged cardiomyocytes at 3–14 days after MI by activating vascular endothelial growth factor signaling. Moreover, enhanced angiogenesis increased cardiomyocyte survival along the endocardium in the ischemic zone and suppressed ventricular remodeling in infarcted hearts. In contrast, cardiomyocytes in the border zone's hypoxic area underwent apoptosis within 12 h of MI, and the border area that was amenable to treatment disappeared. These data indicate that the non-perfused area along the endocardium is a site of active angiogenesis and a promising target for MI treatment.

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Research Background

Myocardial infarction (MI) is a leading cause of death in westernized countries. Catheter intervention therapy during the acute phase reduce the size of the infarct and improve the prognoses of MI patients. However, a subset of patients requires ventricular assistance devices or heart transplantations, because of the extreme impairment of cardiac function. No effective or innovative therapies have been developed for MI since catheter intervention became a widely used treatment. One reason for the lack of adequate alternative therapies is that the target area and cells to be salvaged in the infarcted heart have not been identified. Most newly developed therapies target the interface between the perfused and non-perfused areas of the heart, and they attempt to inhibit cardiomyocyte apoptosis or induce angiogenesis. The spatial and temporal identification of the cells that are amenable to treatment is essential for the development of future and more effective therapies for MI.

Research Results

The area within 100–150 μm of the endocardium was hypoxic with a partial pressure of oxygen that was < 10 mmHg for 2 days after the MI. Surprisingly, primitive vessels developed from the endocardium on day 3 within the ischemic area and they perfused the hypoxic area by circulating oxygenated blood within the LV, which was a new circulatory system that was independent of the coronary circulation. Three-dimensional imaging showed the growth of new vessels from the endocardium that perfused blood in the LV into the heart tissue.

In particular, the expression of VEGF-A increased markedly in the hypoxic area 24 h after an MI was induced. We found that VEGFR2 was expressed at an early stage of angiogenesis, even in the primitive vessels of the endocardium. To confirm the importance of VEGF-VEGFR2 signaling, we suppressed the expression of VEGFR2 on the endothelial cells of the primitive vessels using tamoxifen-induced conditional knockout mice, and found that the new vessels originating from the endocardium were less prominent in the mice that were deficient in VEGFR2 compared with those in the control mice 5 days after the MI. The new circulatory system that is derived from the ventricle is highly dependant on VEGF-VEGFR2 signaling.

To expand the area that was oxygenated from the LV, we applied a higher concentration of oxygen from 1 h to 4 days after the MI was induced. Compared with the mice that were maintained in room air, treatment with 60% oxygen enhanced oxygen diffusion from the ventricle during the early phase of MI, and a wider area of surviving cardiomyocytes was present on day 28. The dilation of the LV was suppressed in the oxygen-treated mice. This finding indicates that the area along the endocardium that contained the surviving cardiomyocytes is an important target for the treatment of MI from the acute phase to the chronic phase. Therapies that suppress apoptosis or induce angiogenesis in this particular area could be applied in combination with therapy comprising a high concentration of oxygen as was applied in this study.

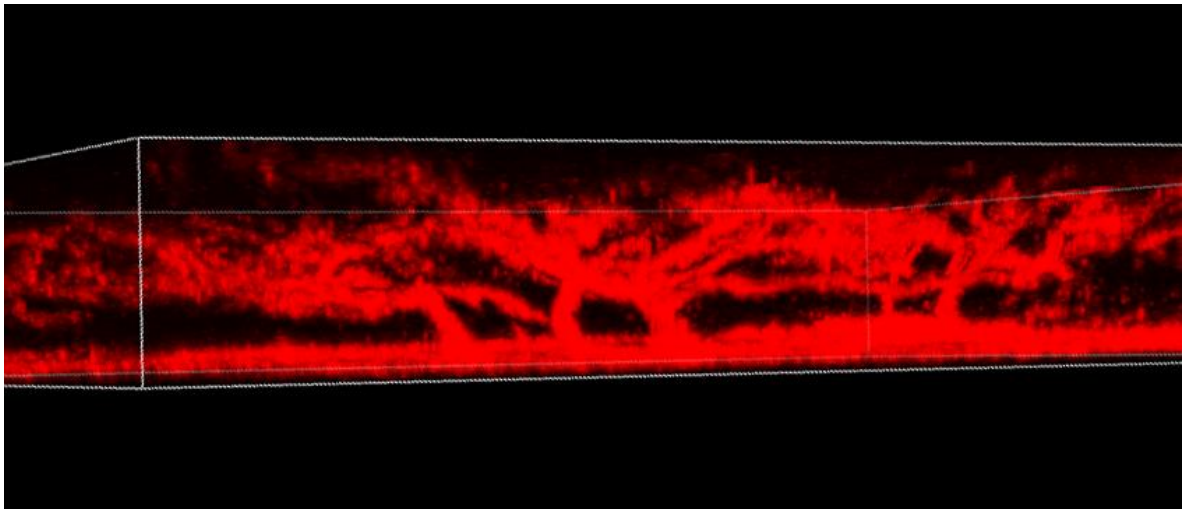

Figure. New vessels developed from endocardium (inferior surface)

Research Summary and Future Perspective

Here we have verified the presence of a novel circulatory system that develops from the LV, which is separate from the coronary circulation, during the pathological conditions associated with MI. Furthermore, our results indicate that the area along the endocardium that is perfused by blood from the LV could be the target for the future treatment of the acute and chronic phases of MI.

Publication

Koichi Kobayashi[1]*, Kengo Maeda[1], Mikito Takefuji[1], Ryosuke Kikuchi[2], Yoshihiro Morishita[1], Masanori Hirashima[3], & Toyoaki Murohara[1]

Affiliations

[1]Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya 466-8560, Japan

[2]Department of Medical Technique, Nagoya University Hospital, Nagoya 466-8560, Japan

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