

Pathophysiology of coronary microembolisation

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The combination of endothelial damage and severe coronary stenosis induces typical cyclic coronary flow variations, characterised by progressively decreased coronary blood flow over several minutes followed by an abrupt increase in coronary blood flow.¹ Such cyclic flow variations are attributed to platelet aggregates² that progressively plug the stenotic epicardial coronary artery segment and are then suddenly dislodged into the coronary microcirculation; aspirin consistently prevents cyclic coronary blood flow variations.³ Cyclic coronary blood flow variations cause decreased regional contractile function in the dependent myocardium⁴ and arrhythmias.⁵

Coronary microembolisation in the absence of coronary stenosis induces a transient decrease in coronary blood flow immediately with the microembolisation followed by a more prolonged increase in coronary blood flow; the hyperaemia is associated with a release of adenosine and prevented by the adenosine receptor antagonist theophylline. Despite the increase in coronary blood flow which most likely results from dilation of the microvessels surrounding the embolised vessel, coronary microembolisation induces myocardial ischaemia, as evidenced by reduced regional contractile function and reduced lactate extraction.⁶ The destruction of free radicals by superoxide dismutase enhances the release of adenosine and the resulting hyperaemia, and attenuates the decreases in regional contractile function and lactate extraction following coronary microembolisation.⁷

INFLAMMATION AND ANGIOGENESIS WITH CORONARY MICROEMBOLISATION

Focal microinfarcts with leucocyte infiltration were found in human postmortem studies as well as in experimental studies using coronary microembolisation and histological analysis of the myocardium. Coronary microembolisation with 25 µm microspheres in pigs induced not only patchy microinfarcts with leucocyte infiltration but also enhanced expression of tumour necrosis factor α (TNFα) in monocytes/macrophages over several days.⁸ Interestingly, both the increased TNFα expression and the angiogenic response in the affected myocardium were inhibited by cyclosporine or dexamethasone.⁸ An inflammation-linked angiogenic response with a coordinated expression of the insulin-like growth factor system was demonstrated in pigs following coronary microembolisation,⁹ confirming earlier studies on collateral growth in conscious dogs with coronary microembolisation.¹⁰

CHRONIC HEART FAILURE BY REPETITIVE CORONARY MICROEMBOLISATION

To avoid excess mortality and to achieve a stable model of heart failure, Sabbah and colleagues developed a chronic dog model of heart failure by multiple sequential coronary microembolisations with microspheres of 70–100 µm diameter. This model is not only characterised by typical clinical signs of heart failure and impaired ventricular function, but also by cardiac hypertrophy and patchy myocardial fibrosis, characteristic increases in plasma atrial natriuretic factor (ANF) and noradrenaline (norepinephrine) concentrations,¹¹ impaired

sarcoplasmic ATPase expression and activity,¹² impaired mitochondrial respiration,¹³ and evidence for apoptosis in regions surrounding patchy fibrosis.¹⁴

CORONARY MICROEMBOLISATION AS A MODEL OF UNSTABLE ANGINA

Recognising the importance of coronary microembolisation in the pathogenesis of acute coronary syndromes and following coronary interventions,¹⁵ we have studied the consequences of intracoronary infusion of microspheres with a diameter of 42 µm for the affected myocardium in anaesthetised dogs. Stepwise intracoronary infusion of microspheres up to a final dose of 3000 spheres/ml baseline coronary blood flow caused an immediate decrease in coronary blood flow upon infusion followed by a more prolonged reactive increase in flow. In contrast, regional systolic wall thickening recovered only partially, but did remain depressed.¹⁶ Moreover, a progressive further decrease in regional systolic wall thickening was seen over several hours following the microembolisation procedure, which was not associated with a decrease in regional myocardial blood flow at the spatial level, which could be resolved by the microspheres technique.

When comparing the consequences of an epicardial coronary artery stenosis on regional myocardial blood flow and contractile function with those of coronary microembolisation at equal levels of contractile dysfunction, the stenosis was characterised by typical perfusion–contraction matching, whereas the coronary microembolisation induced a perfusion–contraction mismatch pattern.¹⁷ Coronary microembolisation caused patchy microinfarction which affected about 2% of the respective myocardium.¹⁸ Less than 0.1% of cardiomyocytes were apoptotic, and apoptotic cardiomyocytes were always associated with the microinfarcts.¹⁸ The microinfarcts were characterised by leucocyte infiltration, including monocytes/macrophages, but the microspheres per se proved to be inert and not chemoattractant *in vitro*.¹⁷ Since there was only little infarcted myocardium and myocardial blood flow was not reduced, we hypothesised that the observed inflammatory response might be responsible for the observed profound regional contractile dysfunction following coronary microembolisation. Indeed, methylprednisolone not only prevented the increased leucocyte infiltration but also the contractile dysfunction.¹⁹

More specifically, we identified a causal role for TNFα in the observed contractile dysfunction. Not only were increased myocardial TNFα concentrations associated with contractile dysfunction following coronary microembolisation, but also intracoronary infusion of exogenous TNFα induced dysfunction in the absence of microembolisation, and conversely pretreatment with TNFα antibodies prevented dysfunction following microembolisation.¹⁸ TNFα was localised in infiltrated leucocytes within and around microinfarcts and also in cardiomyocytes in the viable border zone around microinfarcts. *In situ* hybridisation of TNFα-mRNA identified these viable myocytes as a major source of TNFα in microembolised myocardium.¹⁸ To specify the signal cascade of TNFα induced dysfunction in this model we have further studied the role of

nitric oxide (NO) and sphingosine, known elements of the signal transduction cascade of TNF α in ischaemia–reperfusion injury and chronic heart failure.

Microembolisation increased TNF α and sphingosine contents in the myocardium. Pretreatment with the NO synthase inhibitor N[G]-nitro-L-arginine-methylester attenuated the progressive myocardial contractile dysfunction, and TNF α and sphingosine contents were no longer increased.²⁰ N-oleoylethanolamine, which disrupts the sphingomyelinase pathway by blocking the enzyme ceramidase which catalyses the conversion of ceramide to sphingosine, also abolished the progressive contractile dysfunction following coronary microembolisation; myocardial TNF α but not sphingosine content was increased.²⁰ These results strongly suggest that the microembolisation induced progressive contractile dysfunction is signalled through a cascade with NO located upstream of TNF α and sphingosine located downstream of TNF α .²⁰ NO was obviously derived from endothelial NO synthase, since the expression of inducible NO synthase was not detectable in the microembolised myocardium. Haemodynamically, this experimental model of coronary microembolisation is not only characterised by a perfusion–contraction mismatch pattern, but also by reduced coronary reserve. The reactive hyperaemia after a brief coronary occlusion and the blood flow response to intracoronary infused adenosine were blunted. Also, the inotropic response to intracoronary infusion of dobutamine is diminished in microembolised myocardium.¹⁶

CONCLUSION

Experimental coronary microembolisation has been used in the laboratory animal to mimic clinical scenarios of ischaemic heart disease, from unstable angina to chronic heart failure. Although haemodynamic and morphological features of such experimental coronary microembolisation models were remarkably similar to the clinical situation,^{21,22} it remains unclear whether or not coronary microembolisation is a realistic model of these clinical entities, particularly since the size and number of thromboemboli and associated microinfarcts in the clinical situation are quantitatively unknown and therefore not available for comparison to the largely varying size and number of emboli and associated microinfarcts in the above experimental models.

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