Cardiac sympathetic hyperinnervation after myocardial infarction: a systematic review and qualitative analysis

H.S. Chen1, L. Van Roon1, J. Schoones1, K. Zeppenfeld1, M.C. Deruiter1, M.R.M. Jongbloed1

1Leiden University Medical Center, Leiden, Netherlands (The)

Funding Acknowledgements: Type of funding sources: Public grant(s) – National budget only. Main funding source(s): NWO

Background: Cardiac sympathetic hyperinnervation after myocardial infarction (MI) is associated with arrhythmogenesis and sudden cardiac death. The characteristics of cardiac sympathetic hyperinnervation remain largely underexposed.

Objective: To provide a systematic review on cardiac sympathetic hyperinnervation after MI taking into account: 1. Definition, experimental model and quantification method of hyperinnervation, and 2. Location, amount and timing of hyperinnervation, in order to obtain an overview of current knowledge and to expose gaps in literature.

Methods: References on cardiac sympathetic hyperinnervation were screened for inclusion. The included studies received a full-text review, and subsequently a quality appraisal was performed. Relevant data on cardiac sympathetic hyperinnervation were collected and qualitatively analysed.

Results: Our literature search identified 60 eligible studies performed between 2000 and 2022. Cardiac hyperinnervation is generally defined as an increased sympathetic nerve density or increased number of sympathetic nerves compared to another control group (100%). Studies were performed in a multitude of experimental models, but most commonly in male rats with permanent LAD ligation (male: 63%, rat: 68%, permanent ligation: 93%, LAD: 97%). Hyperinnervation seems to occur mainly in the borderzone. Quantification after MI relied on calculating the nerve density in regions of interest in µm²/mm² (41%) or in percentage of nerve fibers (46%) and the reported amount showed a great variation ranging from 439 to 126718 µm²/mm². Remarkably, cardiac sympathetic hyperinnervation seems to be present at all timepoints starting from 3 days onwards to >3 months without an evident peak, although studies on structural evaluation over time and in the chronic phase were scarce.

Conclusion: Cardiac sympathetic hyperinnervation occurs already at 3 days after MI mainly in the borderzone and remains present at all timepoints. It is most commonly studied in male rats with permanent LAD ligation. The amount of hyperinnervation differs greatly between studies, possibly due to the differential quantification methods. Further studies are required that evaluate cardiac sympathetic hyperinnervation over time and in the chronic phase, in transmural sections, in the female sex, and in MI with reperfusion.