

# New paradigm in graft rejection detection in heart transplantation recipients: diagnostic utility of synchrotron X-ray phase contrast imaging (GRAFT-XPCI) - a multi-centric, prospective, observational study protocol

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**Background:** Graft rejection remains the most important complication after heart transplantation (HTx). Endomyocardial biopsy (EMB) is the gold standard in HTx follow-up, however, conventional histopathological (HP) analysis is limited by tissue damage during preparation, 2-dimensional (2D) analysis, and low inter-observer agreement in rejection grading. X-ray phase contrast imaging (X-PCI) has shown potential for non-destructive imaging of the myocardium, enabling high-resolution 3-dimensional (3D) analysis with fibrosis and fibre orientation quantification.<sup>1</sup>

**Methods and Design:** GRAFT-XPCI is a multi-centric, prospective observational study aiming to prove non-inferiority of X-PCI in graft rejection diagnosis, vs. conventional HP (**Figure 1**). It will include ap-

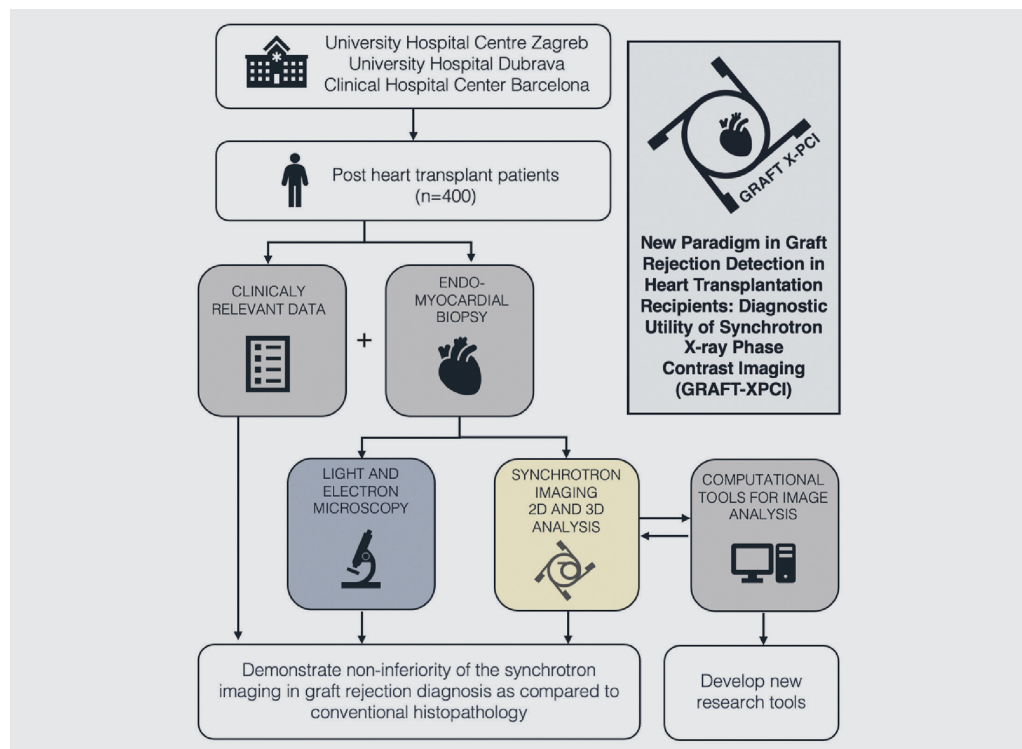


FIGURE 1. GRAFT- X-ray phase contrast imaging study.

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proximately 400 patients in standard post-HTx follow-up at 3 clinical centres: University Hospital Centre Zagreb, Dubrava University Hospital and Hospital Clinic Barcelona. Collected data will include EMB samples, patient history, laboratory, electrocardiogram (ECG), coronarography and echocardiographic data. EMB specimens will be initially imaged by X-PCI at the Paul Scherrer Institute (Villigen, Switzerland), producing digital 3D imaging datasets (at 0.65  $\mu\text{m}$  pixel resolution) for computational analysis, and then prepared for HP microscopy at the University of Zagreb School of Medicine. Three datasets will be generated for analysis - 2D X-PCI dataset, 3D X-PCI dataset, and 2D HP images. Acquired X-PCI images and HP slides will be diagnostically graded (ISHLT 2004. grading system)<sup>2</sup>, comparatively assessed by at least two observers in a blinded fashion, further analysed in conjunction with gathered clinical data. Computer methods for the automatic and semi-automatic analysis of digital image datasets will be developed as an additional output.

**Conclusion:** GRAFT-XPCI will: 1) compare X-PCI and conventional HP in graft rejection analysis, 2) enable insight into structural and pathophysiological processes in graft rejection after HTx, 3) extend the amount of information gained by EMB analysis. The development of new research tools and imaging protocols should widen future research of EMB analysis in various cardiac conditions. This study has been fully supported by the Croatian Science Foundation under the trial registration no. UIP-2020-02-5572.

### LITERATURE

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