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BIORESOURCE PAPER

Interdisciplinary Research on Aortic Valve Stenosis: A Longitudinal Collection of Biospecimens and Clinical Data of Patients Undergoing Transcatheter Aortic Valve Replacement

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The bioresource (>265 patients with >27,600 biospecimens until December 2019; recruitment ongoing) on severe aortic stenosis is of vital importance to improve the still incomplete understanding of its etiology as well as its transition to heart failure. The bioresource contains various biospecimens, standardised clinical and imaging data sets including transthoracic echocardiography, computed tomography and magnetic resonance imaging of the heart. Biospecimen sampling follows the SOP-driven collection scheme of the German Center for Cardiovascular Research (DZHK) for venous blood and urine [1]. In addition, left-ventricular endomyocardial biopsies, rectal swabs and skin biopsies (for subsequent generation of induced pluripotent stem cells) are collected. Data management includes the use of a professional biospecimen management system as well as a Picture Archiving and Communication System (PACS) for imaging data. A Good Clinical Practice (GCP)-conform software for the management of clinical data and a trusted third party for the management of patient identifying data and pseudonyms are in place. Given these conditions, there is a high reuse-potential for biospecimens and data.

Keywords: Heart failure; aortic valve stenosis; biobank; cardiac MRI; echocardiography; left-ventricular cardiomyocytes; human fibroblasts; microbiome

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(1) Bioresource Overview

Project description

Aortic valve stenosis (AS) has become the most frequent valvular heart disease in Europe and North America with a prevalence of 2–7% of the population above the age of 65 years [2]. Pathophysiologically, AS represents an elevated afterload for the left-ventricular myocardium leading to concentric hypertrophy to preserve physiological wall stress (compensated hypertrophy; CH). With ongoing progress of (untreated) valvular stenosis CH can transform to heart failure. For the transition to heart failure and outcome of patients after aortic valve replacement (AVR) the fibrotic load of left ventricle myocardium seems to be crucial [3]. Left-ventricular systolic dysfunction and the patients' symptoms are key factors indicating transcatheter AVR (TAVR) [4].

However, the molecular regulation of the transition from CH of myocardium to heart failure is still poorly understood. Previous studies have focused on endstage failing human myocardium [5], animal models [6] and induced pluripotent stem cells (iPSC) [7] due to a lack of left-ventricular myocardial samples from patients with severe AS. Notwithstanding, all experimental designs lacking direct access to human ventricular myocytes embedded in physiological cardiac connective tissue will be inherently limited in statements on pathophysiology of the transition to heart failure in patients suffering from aortic valve stenosis.

The aim of this project is, therefore, to elucidate the impact of excessive afterload of severe AS on left-ventricular myocardium, its transition to heart failure as well as the recovery from heart failure. The ambition is to build up an infrastructure facilitating interdisciplinary research ranging from clinical research to basic science in the field of aortic valve stenosis and heart failure. Special emphasis will be put on the relatively new disease entity "paradoxical low-flow low-gradient AS".

Classification (1)
Human

Species
Homo sapiens

Classification (2)
Biological samples and associated data

Context
Spatial coverage
Bioresource was collected from patients that underwent TAVR due to severe symptomatic AS at the University Medical Center Göttingen (UMG). Roughly, 90% of UMG patients come from within a radius 90 km around Göttingen (see geographical coordinates). However, patients have been recruited from all over Germany.

UMG, Göttingen, Lower Saxony, Germany: 51°33′03.1″N 9°56′33.0″E

Northern boundary: 52°02′36.5″N 9°33′58.0″E
Southern boundary: 51°00′30.2″N 10°12′10.6″E
Eastern boundary: 51°38′27.3″N 10°42′03.6″E
Western boundary: 51°29′17.3″N 9°07′13.3″E

Temporal coverage
The start of the collection period was 31.01.2017. The collection is ongoing. Based on the current ethics approval and recruitment rate the expected date of last inclusion will be in 2024.

Temporal coverage for accessibility
As approved by the ethics committee, bioresources can be stored for at least 15 years after inclusion. After completion of the study, bioresource can still be used for research in an anonymized form. In case of consent withdrawal, samples have to be anonymized as well.

(2) Methods

Steps
Typically, the patients are admitted to hospital two to three days prior to TAVR. Once the diagnosis of severe symptomatic AS is made and TAVR is indicated by interdisciplinary heart-team, patients can give informed consent to participate in the study. Patients are informed about background, purpose and goals of this study and its ramifications in a personal and elaborate discussion by experienced clinicians who comply with current GCP standards.

Sample collection
Blood and urine
Preinterventionally, a set of biological specimen including venous blood and spontaneously voided urine are collected, processed and stored according to the standard operating procedures (SOPs) of the German Center for Cardiovascular Research (DZHK) [1]. Briefly, 33 ml of venous blood is sampled from a cubital vein in vacutainer tubes (2 serum tubes (7.5 ml), 1 citrate tube (3 ml) and 2 ethylenediaminetetraacetic acid (EDTA) tubes (7.5 ml); all sample tubes are purchased from Sarstedt). 10 ml of spontaneously voided urine are collected in tubes without further additives. In addition, 2.5 ml venous blood is collected in PAXgene blood RNA tubes (Becton Dickinson). The samples are left in vertical position for 30 minutes at ambient temperature. Afterwards, sample containing tubes are centrifuged at 2000 g for 10 minutes or 3000 g for 5 minutes. The supernatant of each tube is aliquoted as follows (see **Table 1**): 20 × serum, 20 × K-EDTA, 8 × Na-citrate, 4 × buffy coat from K-EDTA tubes and 16 × urine; each aliquot has a volume of 300 µl [8]. Blood samples in PAXgene blood RNA tubes are processed as outlined in the manufacturers instructions [9].

Stool samples
Stool samples are obtained in all patients that provided informed written consent to the collection of stool samples and do not fulfill any of the following exclusion criteria: (a) treatment with antibiotics, glucocorticoids or immunosuppressive drugs within the previous three months; (b) acute infection; (c) chronic inflammatory disease; (d) malignancy; (e) need for renal replacement therapy; (f) gastrointestinal surgery within the last three years. Stool samples are collected via rectal swabs (two swabs per patient; eNAT from Copan) for the isolation of microbial DNA and RNA. For the collection, a sterile flocked swab is inserted into the rectum, rotated gently and removed. The swab is immediately placed into a tube containing 1 ml of stabilizer (guanidine-thiocyanate-based medium). The tube with the swab is vortexed for 30 seconds to allow the stool to suspend in the stabilizing medium. Afterwards, the solution is aliquoted (2 × 300 µl aliquots per swab) and stored at –80°C.

Left-ventricular endomyocardial biopsies
According to an elevated surgical risk most patients undergo transfemoral TAVR (tf-TAVR). After successful valve implantation – if consented – five left-ventricular endomyocardial biopsies are taken from the basal anteroseptum by using 7F endomyocardial biopsy forceps (Proflex-Bioptom, Medical Imaging Systems). One of five biopsies is fixed for 24 hours in 4% paraformaldehyde (Roti-Histofix 4%, Carl Roth), washed with Dulbecco's Phosphate-Buffered Saline (# 14190-094, Gibco) and fixed with paraffine. The other four biopsies are immediately preserved in liquid nitrogen and kept at –80°C. Handling of left-ventricular biopsies follows our study specific protocol [10].

Table 1: Overview of the biospecimens, their preservatives, and preservation temperatures.

Biological specimen	Additive/short term preservative	Long term preservation temperature	Number of aliquots à 300 µl	Baseline	6 months follow up	1 year follow up
Venous blood	Serum – silicate	–80°C	20	x	x	x
	Plasma – K-EDTA	–80°C	20	x	x	x
	Plasma Buffy Coat – K-EDTA	–80°C	4	x	x	x
	Plasma – Na-Citrate	–80°C	8	x	x	x
RNA	Paxgene Blood RNA system (BD)	–80°C	1 Paxgene tube	x		x
Spontaneous urine	none	–80°C	16	x		
Left-ventricular biopsies	LN_2	–80°C	4 biopsies	x		
	4% paraformaldehyde (PFA)	Room temperature (PFA-fixed, paraffin embedded)	1 biopsy	x		
Rectal swabs	eNAT (guanidine-thiocyanate-based medium)	–80°C	4	x	x	
Fibroblasts	DMEM + 20% FBS + 8% DMSO	–196°C	8–12 in 2 ml cryo vials	x		

Fibroblasts

At the end of the intervention, a skin biopsy (3–4 mm) is obtained at the catheter access site. The biopsy is placed in Dulbecco's Modified Eagle Medium (DMEM) (Thermo Fisher Scientific, #11960044) containing 200 U/ml penicillin and 200 µg/ml streptomycin (Thermo Fisher Scientific, #15140122) and transferred to the UMG Stem Cell Unit within 48 hours. Biopsies are dissociated streichen using the human whole skin dissociation kit (Miltenyi Biotech, #130-101-540) and the gentleMACS dissociator (Miltenyi Biotech) according to manufacturer's instructions. Cells are plated in cell culture plates and cultured in human fibroblast medium (HFBM) composed of DMEM (Thermo Fisher Scientific, #11960044) supplemented with 10% Fetal Bovine Serum (FBS; Thermo Fisher Scientific, #10270106), 1 × MEM Non-Essential Amino Acids Solution (Thermo Fisher Scientific, #11140035), 2 mM L-Glutamine (Thermo Fisher Scientific, #25030024), 50 µM β-mercaptoethanol (Serva Electrophoresis, #28625), 10 ng/ml basic Fibroblast Growth Factor (bFGF;Peprotech, #100-18B), 100 U/ml penicillin and 100 µg/ml streptomycin (Thermo Fisher Scientific, #15140122) at 37°C with 5% CO_2 atmosphere. Medium is changed every other day.

Stabilization/preservation

See **Table 1**.

Type of long-term preservation

See **Table 1**.

Fibroblasts are cryopreserved in DMEM supplemented with 20% FBS and 8% Dimethylsulfoxide (DMSO; Sigma-Aldrich, #D2650).

Storage temperature

See **Table 1**.

Shipping temperature from patient/source to preservation or research use

All biospecimens are transported at –80°C except for fibroblasts, which are transported in the vapour phase of liquid nitrogen.

Shipping temperature from storage to research use

All samples are transported to researchers on dry ice, except for cells, which are transported in the vapour phase of liquid nitrogen.

Quality assurance measures

Venous blood samples and urine are screened for abnormalities such as hemolysis. Potential abnormalities are documented in project-specific quality assurance and documentation forms [11]. Fibroblast cultures are analyzed for morphology, proliferation and cell viability. Deviations from SOPs are being documented using the Sample Preanalytical Code (SPREC) [12–14] in the biospecimen management system.

Source of associated data

After admission to the hospital patients with suspected severe symptomatic AS are screened for enrolment. If the patient consents to the study and the severe AS is confirmed according to the current guidelines of the European Society of Cardiology, then a basic set of clinical data [15] is collected. This basic set includes anamnesis, physical examination and imaging data. It is being obtained and documented by experienced physicians in the field of valvular heart diseases. Imaging data cover

transthoracic echocardiography, computed tomography and cardiac magnetic resonance imaging. Additionally, quality of life is assessed by standardized 6 minute walking test [16], New York Heart Association (NYHA) classification and Minnesota Living with Heart Failure Quality of Life Questionnaire. Periinterventionally, complications according to Valve Academic Research Consortium (VARC)-2 defined criteria [17] are documented. **Table 2** gives an overview of the type and time points of collection of clinical data.

Clinical data are documented in electronic case report forms (eCRF) in a professional, entirely web-based, and GCP-compliant electronic data capture system (secuTrial from interActive Systems). Due to ongoing data and sample analysis, the database is constantly growing.

In the future, data from analyses of biospecimens will be fed back to the project. Thus, the dataset will be further enriched, e.g. by RNA and DNA profiling, which was performed by next generation sequencing in a subset of samples to study molecular aspects of heart failure progression.

Ethics Statement

The study was approved by the ethics committee of the medical faculty in Göttingen (reference number 10/5/16). The first approval was limited to 120 patients obtaining left-ventricular biopsies. In June 2019, an extension for another 103 patients was approved.

Constraints

It is difficult to obtain control samples (i.e. left-ventricular endomyocardial biopsies) from non-failing myocardium for research purposes. The current ethics approval does not comprise myocardial biopsies from healthy patients. Patients with altered mental status, dementia or having a legal guardian for any other reason are excluded from the study. In order to ensure that patients comprehend the entire scope of the study, patients who do not speak German fluently are excluded.

(3) Bioresource description

Object name

UMG Biobank (Central Core Facility of the University Medical Center Göttingen (UMG)).

Bioresource name

SFB 1002: Venous blood (serum, EDTA, Citrate, PaxGene), spontaneously voided urine, rectal swabs, endomyocardial left-ventricular biopsies, fibroblasts.

Bioresource location

The bioresource of the AS study is located at the UMG, where patients are being recruited. UMG is part of the Georg-August-University Göttingen in Germany. The biospecimens have been collected in the Clinic for Cardiology and Pneumology and stored in the central core facility UMG Biobank. The IT-infrastructure for data management was set up by the Department of Medical Informatics and data are stored within IT systems hosted and operated by the medical computing center of the UMG.

Bioresource contact

biobank@med.uni-goettingen.de

Table 2: Overview of the clinical data collected.

	Baseline	Clinical discharge	30 days after intervention*	6 months follow up	1 year follow up	2 years follow up*	3 years follow up*	4 years follow up*	5 years follow up*
Clinical basic data set	x			x	x				
transthoracic echocardiography	x			x	x				
12-lead suface ECG	x			x	x				
Cardiac MRI	x				x				
Cardiac computed tomography	x								
VARC-2 defined criteria	x	x							
6 minute walking test	x			x	x				
NYHA class	x		x	x	x	x	x	x	x
Minnesota Living with Heart Failure Questionnaire	x		x	x	x	x	x	x	x
Re-hospitalisation			x	x	x	x	x	x	x
Mortality	x		x	x	x	x	x	x	x

* Assessed via a phone visit.

Bioresource URL
biobank.umg.eu

Identifier used
Not applicable

Bioresource type
Cardiology, Cytology, Histology, Radiology, Thoracic Surgery, Clinical Chemistry, Human Genetics, Pathology.

Type of sampling
Sampled in clinical care and in a research protocol.

Anatomical site
Endomyocardial biopsies are harvested from the apex of the left ventricle.

Disease status of patients/source
Patients suffering from symptomatic severe AS that are scheduled to undergo TAVR.

Clinical characteristics of patients/source
Patients that are scheduled to undergo TAVR for severe symptomatic AS represent a high-risk collective and are characterized by old age and a high number of co-morbidities.

Size of the bioresource
Currently, more than 265 patients are included in the study resulting in ~27.600 aliquots. Endomyocardial biopsies have been harvested from 120 patients, the ethics approval for another 103 patients was just received. However, several samples (blood and myocardial biopsies) have already been distributed to various projects. Therefore, the number of available samples is subject to continuous changes.

Vital state of patients/source
Alive

Clinical diagnosis of patients/source
Symptomatic severe AS according to current guidelines.

Pathology diagnosis
ICD-10: I35.0

Control samples
To this date, there are no control samples available.

Biospecimen type
See **Table 1**.

Release date
The bioresource is available.

Access criteria
To access the bioresource, researchers must write an informal request summarizing their project, the research question and the expected results. For the experiments, the number of patients per AS sub-group as well as the required biospecimen types (quantity and quality) have to be specified. Biospecimens, which could be used alternatively should be specified as well. It is also possible to get datasets only.

The request should be addressed to the UMG Biobank (biobank@med.uni-goettingen.de), who will forward it to the respective Use and Access Committee. Requests are debated in monthly meetings of the local and project-specific Use and Access Committee. If all members approve the request and sufficient bioresource is available, biospecimens will be transferred via the UMG Biobank accordingly. Bioresource that was not used by the applicant but had to be transferred due to varying aliquot sizes has to be returned to the UMG Biobank. The applicant is responsible to ensure appropriate transportation. Also, the applicant is expected to collaborate with local researchers where suitable. Prior to any publication based on samples from this bioresource the publication must be consented by our publication committee.

(4) Reuse potential

Fibroblast cell lines derived from skin biopsies of patients can be re-programmed into induced pluripotent stem cells (iPSCs). These iPSCs can then be differentiated to iPSC-cardiomyocytes or to iPSC-cardiac fibroblasts for further analyses offering a wide reuse potential.

Researchers can request clinical and imaging data as well as biospecimens as defined above (see Access criteria). Biospecimens are transferred via the UMG Biobank in the aliquots specified above (see biospecimen type). If samples have been transferred in quantities exceeding the researchers needs, the spare material has to be returned to the UMG Biobank. Transport times, defrosting time and process as well as the type of analysis carried out will be documented. Given the exact documentation systems in place, samples and data show a high-reuse potential. When applying for samples, researchers should indicate whether or not reused samples fit the purposes of their experiments.

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Competing Interests
The authors have no competing interests to declare.

Author Contributions
Bo E. C. Beuthner and Rodi Topci shared first authorship.

Author Roles
Beuthner, B. E. C.; Topci, R (clinical investigators, echocardiography); Puls, M (echocardiography supervisor); Toischer, K (proteomics, transcriptomics); Schuster, A (cardiac MRI); Valentova, M (microbiome); Zeisberg, E (histology); Cyganek, L (stem cell unit); Jacobshagen, C (principal investigator, co-chairman of the project); Derks, M; Seelke, S (bioresource manager); Franke, T (IT-infrastructure manager); Hasenfuss, G (chairman); Nussbeck, SY (bioresource manager, IT-infrastructure manager).

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