Tailored acute heart failure treatment
The impact of age and comorbidity on new pharmacological treatment models

1.1 Relevance relative to the call for proposals
This project is initiated from the UNN/UiT collaboration with a clear translational approach. The potential impact is development of new therapies for patients in cardiogenic shock.

1.2 Scientific part

Background and state of knowledge
Revascularization therapy following acute myocardial infarction (AMI) has reduced mortality from approximately 30% in the 1960s to 6-7% at present. However, the mortality observed in AMI patients with cardiogenic shock (CS) exceeds 50% and has hardly improved, despite the introduction of modern treatment strategies. Most CS-related deaths occur during the first 48 hours. Thus, instant simple bedside diagnostic predictors could help optimize therapy for these patients. Data from the SHOCK trial revealed that the stroke volume (SVi) is the strongest early hemodynamic predictor of mortality, which suggests that a low cardiac output (CO) alone is not detrimental to the outcome. However, if the CO is low despite a compensatory tachycardia, patients have a poor prognosis. Tachycardia shortens the diastolic time interval for ventricular filling, and thus, the early filling rate must increase to maintain the stroke volume. A main determinant for rapid filling is the myocardial capacity required to generate a negative pressure in the left ventricle and by that “suck” blood into the ventricle, i.e., diastolic suction. Diastolic suction is driven by elastic recoil in the myocardium. During ejection, the heart compresses the ventricular lumen beyond the equilibrium resting shape. In the following diastole, the ventricle spontaneously expands as the intrinsic myocardial tension is released. Suction is coupled to contractility in that enhanced contractility squeezes the ventricular cavity further away from the passive shape of the relaxed ventricle. We hypothesize that suction might be impaired in acute global ischemia as has been shown in other states of contractile impairments. At present, the compensatory tachycardia resulting in diastolic suction–heart rate mismatch is an unexplored area of the circulatory response to acute heart failure.

Tachycardia may also impair cardiac efficiency. The ischemic heart has a limited coronary reserve with hampered vasodilation i.e a reduced hyperemic response. Coronary filling occurs in diastole and is thus inversely related to heart rate as tachycardia reduces the diastolic time interval. In addition, heart rate reduction is one of the most important energy-saving maneuvers and can be achieved by β-receptor-blocking substances. However, patients in CS with primarily reduced contractility do not tolerate the negative inotropic effect of β-blockers, leading to further aggravation of the shock. An ideal drug in this setting should selectively reduce the heart rate without affecting the contractile function of the heart. Ivabradine is one such drug and has been approved for clinical use in patients with stable angina. Ivabradine reduces action potential frequencies by inhibiting the I_{if} channels in the sinus node and thereby decelerates the spontaneous depolarization of pacemaker cells, leading to a lower heart rate. Theoretically, the combined use of ivabradine and an inotropic agent (e.g., dobutamine) should enable us to uncouple the heart rate from the contractile force of the heart. We hypothesize that this cocktail might optimize the diastolic function in an ischemic heart.

The use of catecholamine and its synthetic derivatives in the treatment of acute heart failure is controversial (ESC guideline recommendation; 2b). In chronic heart failure, adrenergic drugs increase mortality by inducing myocardial oxygen wastage and arrhythmia. This observation has led to development of new inotropic agents with alternative mechanisms of action. Omecamtiv mecarbil (OM) is a novel synthetic cardiac inotrope that acts by stimulating myosin-ATPase activity. We recently showed that OM acts similarly to dobutamine + ivabradine (Dobut+Iva) by increasing the ejection fraction without increasing the heart rate. However, the drug’s inotropic profile is...
different: dobutamine acts by increasing the speed of contraction\textsuperscript{16}, whereas OM acts by prolonging the systolic ejection time\textsuperscript{14}. This reduced diastolic filling time may be of concern in conditions of tachycardia. Interestingly, a recent study\textsuperscript{17} on a new compound, Myk-461, showed that it exhibits therapeutic potential in hypertrophic cardiomyopathy, as recognized by a severe diastolic constraint. Myk-461 is a specific cardiac myosin inhibitor and thus acts in an opposite manner to that of omecamtiv. We hypothesize a therapeutic principle of myosin activation in patients with severely dilated ventricles. In contrast, myosin inhibition should be attempted in acute heart failure therapy for patients with a restrictive filling pattern similar to that observed in hypertrophic ventricles.

The safety and efficacy of the therapies used for CS patients is not well documented. These patients are in an immediate life-threatening situation, which makes enrollment in randomized clinical trials difficult. Clinically relevant, large-animal models are therefore crucial for validating new and established therapies. A major obstacle is that these animal models often have a different disease background compared to patients. Acute heart failure (AHF) and CS are usually induced and studied in healthy juvenile animals. Patients however, are usually older with a history of chronic cardiovascular disease. Thus, an aging large-animal model with chronic heart failure subjected to acute myocardial ischemia would be an important tool in assessing new therapies for CS and AHF.

### Approaches, hypotheses and choice of method

**Objective**

The main objective of the study is to validate new therapies for diastolic dysfunction in acute heart failure. We will tailor this treatment by taking into account \textit{existing chronic heart failure and old age}. Thus, the first step is to expand and establish the following four groups of pigs in our laboratory:

- Healthy juvenile
- Juvenile with LV hypertrophy by aortic constriction
- Healthy elderly
- Elderly with LV hypertrophy by aortic constriction

**New therapies**

We hypothesize that these models have hearts with distinct metabolic and morphologic properties. Novel therapies following acute myocardial ischemia should be assessed in these animals. The focus should be the combination of myosin activation/deactivation with guideline inotropic support and the selective control of the heart rate through the following:

- Myosin activator (omecamtiv) combined with dobutamine;
- Myosin inhibitor (myk-461) combined with dobutamine; and
- Selective control of tachycardia with ivabradine.

**Endpoints**

- Optimizing diastolic function in acute heart failure (protocol I)
- Efficacy of prolonged treatment in acute heart failure (protocol II)
- Optimizing cardiac energetics in acute heart failure (protocol III)

**Novelty**

This study will conduct the first assessment of new therapies for post ischemic acute heart failure using a clinically relevant large-animal model with existing comorbidities. Second, this study will perform the first assessment of the stimulation/inhibition of the contractile filaments combined with conventional inotropes that increase intracellular calcium. We believe that this approach will provide a unique tool for the optimization of the systolic pump function and the simultaneous improvement of the diastole in severe post-ischemic cardiogenic shock.
Establishment of a pig model with aortic constriction

The American Heart Association has recognized the importance of establishing clinically relevant large-animal models of heart failure. They argue that a relevant model left ventricular hypertrophy (LVH) that replicates human aortic stenosis (AS) should include the following: 1) a slowly evolving LV-aortic pressure gradient; 2) an initial development of LVH with increased myocyte cross-sectional area, myocardial fibrosis, and normal ejection fraction; and 3) progression of myocardial fibrosis and diastolic dysfunction resulting in increased filling pressures that lead to left atrial enlargement and eventually reduced systolic function with the development of HF symptoms. Very few reports exist on large-animal models of AS. The feasibility of this protocol, however, should be reasonable because aortic banding is frequently conducted successfully in rodents. We aim to establish a model through aortic constriction in juvenile pigs, as described by Ye et al. The pigs will be subjected to a minimal right thoracotomy in the third intercostal space at an age of 1–2 months. The ascending aorta, 1–2 cm above the aortic valve, is encircled with a polyethylene band that is tightened to reach a peak systolic pressure gradient across the narrowing aorta of 60–70 mmHg. The chest is then closed, the pneumothorax evacuated, and the animals are allowed to recover. In this model, left ventricular hypertrophy (LVH) will occur progressively as the area of aortic constriction remains fixed in the face of normal body growth. Ye et al reported no mortality with this severe model. Two months after aortic banding, all of the animals developed a substantial left ventricular hypertrophy. Approximately half of these animals develop clinical heart failure with ascites and signs of cyanosis, whereas the other half of these animals only develops a compensated LVH. This model fulfills most of the recommendations provided by AHA experts. With the establishment of this model, we would subject the animals to post-ischemic acute heart failure using our established test battery ref. This model is a cornerstone in our lab with the primary endpoint of assessing the impact of new therapies on cardiometabolic function. We have established four main methods for this assessment: cardiac efficiency, mitochondrial function, sublingual microcirculation and contractile function. These methods are described in the planned protocols below.

Elderly pig model

We have made an agreement with a commercial supplier (Ellegaard, Denmark) to ship elderly Gottingen minipigs that have completed their reproductive period. These pigs are 6–8 years of age, which corresponds to a human age of approximately 60 years. The animals have hormone levels and systemic organ reserve similar to that observed in a typical patient with acute heart failure. The purchase of these animals represents a substantial cost but will be a crucial bridge for translating the findings from our large-animal model to clinical practice. In a subgroup of these pigs, aortic constriction will be performed as described above.

Protocol I

Aim: Assess the impact on post-ischemic diastolic function of the combination of myosin activation/deactivation with guideline inotropic support and ivabradine. Rationale: We hypothesize that both dobutamine and omecamtiv improve diastolic suction by increasing the elastic recoil in early diastole. We recently showed that in healthy pigs, these treatments increase the ejection fraction by systolic unloading and thus potentially generate restoring forces in the myocardium. In contrast, we hypothesize that omecamtiv may impair the late diastole. We have shown that omecamtiv induces resting myosin ATP activity, which suggests a continuous intrinsic myofilament activity that may increase passive stiffness in the late diastole. The sujection of elderly pigs with preexisting LVH and diastolic dysfunction to acute myocardial ischemia should substantially challenge diastolic function. In this setting, the combined use of dobutamine and Myk-461 may be superior.

Methodology: Following induction of ventricular hypertrophy with aortic banding, we will use our open-chest pig model with acute left ventricular (LV) dysfunction by microembolization. We will investigate the intrinsic effects of heart rate, load and contractility on early (suction) and late (compliance) diastolic function. Diastolic suction will be assessed using the transmitral pressure difference (PDmitral) and delayed long-axis lengthening (é-delay).
potential (RFP)\textsuperscript{23} and Tau. The late diastolic function will be assessed by the end-diastolic LV pressure-volume relationship (EDPVR) and LV operating chamber stiffness (KVL) (Figure 2). **Endpoints:** Measures of diastolic function, including validation of the novel non-invasive index (é-delay) of early relaxation.

**Pilot study**
To test the feasibility and reproducibility of protocol I, we recently performed a pilot study (Figures 1 and 2). In eight pigs with myocardial ischemia, we simultaneously measured the cardiac dimension (sonometric crystals), mitral-inflow (conductance-catheter) and pressure (micromanometer) in all four cardiac chambers at varying heart rates and preload conditions. The preliminary data indicate that the é-delay is a sensitive index for assessing intrinsic early relaxation in the myocardium and is reduced by ischemia. The operating chamber stiffness (KLV) (Figure 2) was markedly elevated in ischemia independently of preload, which indicates that passive stiffness constrains ventricular filling in acute ischemia.

Figure 1: Actual tracing from one pig. E and é are derivatives of the LV volume (conductance) and long-axis strain (crystals). The pressure difference between the atrium and ventricle (PD\textsubscript{MITRAL}) is the true driving force of diastolic filling.

Figure 2: Typical pressure volume loops from healthy (black and grey) and acute heart failure (colors) animals at varying heart rates and preloads. KLV is defined as the pressure rise/filling in diastole after the time of minimal pressure. KLV is considered a robust index of passive stiffness. As observed in the left figure, KLV is increased in ischemia and is independent of the load and heart rate.

**Preliminary data**

Figure 3: Preliminary data showing examples of the left ventricular pressure-volume relationship. The left panel shows the pre-(dotted line) and post-ischemia (solid line) data. The middle panel shows the data obtained after treatment with omecamtiv mecarbil (OM, blue line) compared with that observed in untreated ischemia. The right panel shows the data obtained after treatment with dobutamine combined with ivabradine (D+I, yellow line) compared with that observed in untreated ischemia. These data indicate that only dobutamine combined with ivabradine is able to restore the stroke volume. Of note, these experiments are performed in juvenile pigs without chronic heart failure.
Protocol II

Aim: Validate the efficacy and safety of altering myosin activation combined with dobutamine and ivabradine in an experimental model of prolonged cardiogenic shock.

Rationale: Dobutamine + ivabradine will reverse the downward spiral of tachycardia and declining stroke volumes by optimizing the contractility-heart rate matching\textsuperscript{15}. Specific myosin activation (omecamtiv) will unload the heart to pre-ischemic levels without increasing the heart rate. However, an increase in passive stiffness would prevent restoration of the stroke volume due to impaired ventricular filling\textsuperscript{14}. Inhibition of myosin ATPase (Myk-461) combined with dobutamine may be beneficial to an elderly hypertrophic heart with a predominant diastolic constraint.

Methodology: Young and old pigs with and without aortic constriction will be used. We will use our minimally invasive pig model of post-ischemic CS\textsuperscript{20}. We recently showed that our pig model fulfills the hemodynamic and metabolic characteristics for clinical cardiogenic shock with elevated filling pressure (MPAP), systemic hypotension (MAP), low cardiac output and tissue hypoperfusion (venous saturation) during the first 12 hours\textsuperscript{20}. In untreated animals, a progressive sinus tachycardia and a corresponding reduction in stroke volume are observed\textsuperscript{20}, which makes the model particularly suitable for testing the hypotheses in protocol II. We will use vascular catheters (Swan-Ganz) for metabolic and hemodynamic monitoring. To assess contractility, we will use an LV pressure-volume catheter. In addition, echocardiography with Doppler examination of the mitral inflow (E), ventricular flow propagation, tissue Doppler (\(e\)) of the mitral ring and color-coded two-dimensional tissue Doppler imaging of the LV, which are non-invasive indices of suction, will be obtained from a transdiaphragmatic apical view. Sublingual microcirculation will be assessed by our recently established protocol\textsuperscript{21}. At the end of the experiments, tissue biopsies from the kidney, liver, intestine and heart will be harvested for mitochondrial studies and proteomics analysis. Using this pig model of cardiogenic shock, we recently showed that mitochondrial respiration from the liver and kidney of untreated animals is a sensitive marker of systemic hypoperfusion\textsuperscript{20}.

Endpoints: Measures of stroke volume (surrogate predictor of mortality\textsuperscript{4}), indices of diastolic function, metabolic status (\(D\)O\textsubscript{2}, SVO\textsubscript{2}, plasma lactate and base excess), sublingual microcirculation, and mitochondrial function (viability, respiratory capacity and ROS production).
Protocol III

Aim: Determine the energetic profile of Dobut+Iva and myosin activation in hypertrophic heart failure, particularly in acute myocardial ischemia.

Rationale: We recently showed that Dobut+Iva is energetically neutral, whereas omecamtiv induces myocardial oxygen wastage mediated by hyperactivation of resting myosin ATPase\(^{14,15}\) (Figure 4). Again, these protocols are performed in juvenile healthy pigs. These animals are highly responsive to β-adrenergic stimuli, resulting in a substantial enhancement of contractility at a very low dobutamine dosage (2 µg/kg/min). We previously showed that a more clinically relevant dosage (10 µg/kg/min) induces myocardial oxygen wastage in these pigs\(^{16}\) (Figure 5). However, this dosage led to a profound overtreatment of cardiac function way beyond the target levels\(^{16}\). Such hemodynamic overshoot may not necessarily occur in a hypertrophic failing heart because de-sensitization of the β-2 receptor is a hallmark in clinical heart failure\(^{24}\). Dobutamine also alters the myocardial metabolism by β-3-stimulated lipolysis, which impacts cardiac efficiency. Regarding omecamtiv, our observation of myocardial oxygen waste\(^{14}\) differs from that obtained in a dog study with pacing-induced heart failure\(^{25}\). In this study, the authors suggest that omecamtiv improves cardiac efficiency. The main difference between these studies is that we used a previously healthy animal subjected to acute heart failure. In contrast, Shen et al\(^{25}\) used a chronic dog model of pacing-induced heart failure. Thus, a model integrating chronic and acute heart failure is warranted.

Methodology: The assessment of in vivo cardiac energetics is a major area of expertise in our laboratory\(^{16,26}\). An open-thorax pig model will be used for this purpose. In brief, a, dual-field, combined pressure-conductance catheter is inserted into the left ventricular cavity to obtain measurements of cardiac work. Transit-time flow probes are placed on the coronary arteries and pulmonary trunk to measure the coronary blood flow and cardiac output, respectively, and myocardial venous blood is drawn from a catheter placed in the great cardiac vein via the coronary sinus. The cardiac efficiency is assessed from multiple recordings of varying steady-state ventricular mechanical work levels, and the myocardial oxygen consumption is measured simultaneously. Different work levels are produced through the stepwise inflation of a balloon catheter in the inferior caval vein. The relationship between the total mechanical work and MVO\(_2\) describes the heart efficiency. To avoid methodological bias, the MVO\(_2\) will be compared against several estimates of the total LV mechanical work: pressure-volume-area (PVA), tension-time index (TTI) and total-mechanical-energy (TME)\(^{16}\). In the same animals, the myocardial energy status will be assessed via the pyruvate and lactate oxidation rates using hot isotopic tracers\(^{14,26}\). Endpoints: Measures of cardio-metabolic efficiency (TTI/PVA-MVO\(_2\)), mechanical (SW\(_{EFF}\)) efficiency, myocardial uptake and oxidation rates of glucose, fatty acids and lactate.

![Figure 5: Data of cardiac efficiency from typical experiments performed in our recent studies\(^{14-16}\). The total mechanical work (x-axis) is related to the myocardial oxygen consumption (y-axis) over a wide range of workloads. A leftward and upward shift indicates inefficiency by excessive MVO\(_2\) at comparable workloads. The left panel shows that ivabradine has a neutral effect on efficiency\(^{15}\). The middle panel shows no effect on cardiac efficiency at a low dose of dobutamine (2 µg/kg/min, Dobut LD), whereas a substantial oxygen wastage was observed at 10 µg/kg/min (Dobut HD)\(^{16}\). The right panel shows myocardial oxygen wastage induced by omecamtiv (OM)\(^{15}\). Again, all of these studies were performed in juvenile pigs without chronic heart failure.](image-url)

Statistics and sample size

6
Based on pilot experiments and our previous protocols\textsuperscript{14,16,26}, we believe that the interventions in the protocols have an effect size (Cohen d) on the hemodynamic parameters of approximately 1 and that the biochemical data (protein expression, mitochondrial respiration, etc.) have an effect size greater than 1, as calculated with G * Power. A group size of 12 animals may reveal a difference in the relevant parameters of approximately 12-40% with a statistical power of 0.9 and p <0.05. Based on the group design, mixed-model ANOVA with post-hoc correction for multiple groups and repeated measurements will be used for the statistical analyses.

Project plan, project management, organization and cooperation
The project plan has been included in the grant application form.

Lab
We have an in-house, clinically relevant large-animal laboratory with a persistent research focus on new therapies for acute heart failure. The simultaneous surveillance of up to three anaesthetized pigs for 24 hours gives us the unique capacity to mimic clinical CS as it is treated in hospital intensive care units (ICUs). In this model, we mirror the clinical setting (hypotension, tissue hypoperfusion, plasma biomarkers and echocardiography indices) to validate unconventional therapies for CS\textsuperscript{20}. The induction of aortic constriction and postoperative surveillance and care will be performed at the Artic Biology facilities, which are located adjacent to our lab. This facility, which is unique in the world, included offices, operating rooms, laboratories, and animal rooms, in an area of approximately 2,700 m\textsuperscript{2}. The buildings are located within a fenced area greater than 50,000 m\textsuperscript{2} that also includes pens for the holding of experimental animals. The facility is approved by the Norwegian Food Safety Authority for the maintenance of a variety of animals for research purposes. Arctic biology facility houses the Artic Animal Physiology research group, with which we have a history of excellent collaboration.

People
Principal investigator (Ole-Jakob How) is a cardiovascular physiologist with a research focus on new treatment strategies targeting myocardial mechanics and metabolism in acute heart failure. Throughout his career, How has acquired in-depth theoretical knowledge on the hemodynamics, cardiac mechanics and energetics necessary to address the hypotheses described in this proposal. Additionally, How has extensive practical experience in performing complex cardiovascular protocols in large-animal models. In the last five years, How has participated in/performed more than 300 cardiac surgery experiments. At present, How has published 13 papers on these models.
Local project collaborator (Prof. Truls Myrmel) is a cardiothoracic surgeon with a persistent research focus on new treatment strategies for acute heart failure. The PI also strongly collaborates with Myrmel (13 co-authored studies), which should facilitate the translational goals described in this proposal.
Local project collaborator (Prof. Ellen Aasum) is a cardiovascular physiologist with a specialization in cardiac metabolism. Assum’s laboratory has extensive experience with isolated working mice hearts. This model would complement the differentiation of the systemic effects observed in the pig model compared with the direct cardiac effects of the suggested treatment. The PI has an established collaboration with Professor Aasum, as observed by 10 co-authored manuscripts.
International collaborator (Prof. Frank Spinale), School of Medicine, University of South Carolina, USA, is one of the preeminent scientists in the world on integrative experiments using large animals. Spinale has been instrumental in developing the clinically relevant pig model of aortic constriction\textsuperscript{27}. Spinale has agreed on consulting and has already provided us with invaluable methodology including a detailed movie of the surgical procedure. The successful postdoc candidate and the PI will spend one year in professor Spinales laboratory to gain expertise in establishing the banding model including surgery and postoperative care. Please see invitation letter attached.
1.3 User participation
Our laboratory has previously used healthy juvenile pigs to validate new therapies for cardiogenic shock. However the diseases affected people of various backgrounds. They may be relatively young and healthy, or older with a history of cardiovascular disease and other comorbidities. The inclusion of older animals and with LV hypertrophy by aortic constriction is motivated by many fruitful discussions between P.I. and a patient relative who died of cardiogenic shock at UNN in 2012. Here are Frode Adolfsens own words (in Norwegian): "Min far døde på UNN Tromsø, som følge av en hjerteflimmer. Fem dager før ble han innlagt ved UNN, Narvik på grunn av et hjerteinfarkt. Der fikk han en medisin som løste opp blodproppen. Han måtte imidlertid hasteopereres på UNN, Tromsø fordi en blodåre i hjertet sprakk. Etter operasjonen var han veldig dårlig og ble liggende flere dager på intensivavdelingen, men ble gradvis noe bedre. Det var derfor et sjokk når de ringte fra sykehuset og fortalte at han var død. Mitt inntrykk er at både han og vi ble godt ivaretatt, og at han fikk omfattende og avansert behandling. Jeg har satt stor pris på de oppklarende samtaler med legene som behandlet han. I ettertid har jeg diskutert mine med Ole-Jakob (P.I.) hvorfor det gikk som det gikk, og hva kardiogent sjokk egentlig er. Jeg har også lest gjennom prosjektet, og etter det jeg forstår veldig relevant for det min far opplevde. Selvfølgelig er det satt å tenke på at dersom min far hadde klart seg gjennom den første uken etter operasjonen, så hadde prognosene vært relativt gode. Jeg håper at dette prosjektet kan gi svar på noen av spørsmålene og skreddersy behandling til den enkelte pasient. Jeg håper dette vil være med på og berge liv til pasienter i kardiogent sjokk i fremtiden”

1.4 Key perspectives and compliance with strategic documents

Compliance with strategic documents
Acute heart failure and diastolic dysfunction are cardiovascular diseases with poor prognoses in which the underlying pathophysiology is, to a large extent, unknown. Health authorities of northern Norway (Helse-Nord) have identified cardiovascular disease as a dedicated research area.

Relevance and benefit to society

| Clinical relevance – a case report | A woman (60 years of age) arrives at the hospital with an acute ST-myocardial infarction. She is immediately subjected to percutaneous coronary intervention (PCI) for revascularization of a coronary main stem occlusion. In the next hour, her systolic blood pressure drops below 90 mmHg with accompanying signs of tissue hypoperfusion. In the intensive care unit (ICU), a Swan Ganz catheter is placed, and fluid/diuretic therapy is optimized. In an attempt to improve her cardiac index of 1.8 m² and her left ventricular (LV) filling pressure of 21 mmHg, stepwise dobutamine infusion and mechanical support with aortic balloon counter-pulsations are performed. However, her cardiac output remains inadequate, and no resolution of her metabolic acidosis is detected. Additionally, a progressive sinus tachycardia of 130 bpm has become a major problem because the short diastolic time severely impairs ventricular filling and coronary perfusion. How should this patient be treated? |

Our proposed model combining chronic and acute heart failure is unique and highly clinically relevant. As a result, we may increase our understanding of the pathophysiology of cardiogenic shock, which may have a direct effect on new therapies for patients such as the woman described above.

Environmental impact
The expected results of this project have no environmental implications.

Ethical perspectives
Animal research always has ethical considerations. In addition, strong surveillance and animal care are mandatory, particularly in chronic protocols. These issues will be addressed based on the expertise exhibited by the Arctic Biology Facility. All experimental protocols shall be approved by the steering
committee of the National Animal Research Authority (NARA) and will be conducted in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Gender issues (Recruitment of women, gender balance and gender perspectives)
Our research group includes both men and women and comprises a mix of senior and junior researchers. At present there is approximately 60% women in this milieu. Both genders are included in the collaborators. The selection of the postdoc candidate will be conducted in accordance with the university’s policy on gender and ethnicity equality. Pigs of both genders will be used in the protocols. Of particular interest would be studying the elderly female minipigs subjected to aortic constriction. We believe that this combination should have the most profound diastolic dysfunction.

1.5 Dissemination and communication of results
The target group for communicating the outcome of this project is primarily the scientific community. The research group has been successful in publishing our work in high-ranking journals. We will strive to maintain this standard. The results from each of the described protocols will be submitted as papers to high-impact scientific journals. During the progression of each study, results will be submitted to international conferences, such as the meetings of the American Heart Association, the European Society of Cardiology and the Cardiovascular System Dynamics Society. The results will also be presented at national meetings; lectures will be given at hospitals and research institutes nationally and internationally. Important results will be communicated to the mass media.

References:


