

# LUND UNIVERSITY

### Effects of food intake on echocardiographic measurements

Gårdinger, Ylva

2024

Document Version: Publisher's PDF, also known as Version of record

#### Link to publication

*Citation for published version (APA):* Gårdinger, Y. (2024). *Effects of food intake on echocardiographic measurements*. [Doctoral Thesis (compilation), Department of Clinical Sciences, Malmö]. Lund University, Faculty of Medicine.

Total number of authors:

#### General rights

Unless other specific re-use rights are stated the following general rights apply:

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights. • Users may download and print one copy of any publication from the public portal for the purpose of private study

or research.

- You may not further distribute the material or use it for any profit-making activity or commercial gain
   You may freely distribute the URL identifying the publication in the public portal

Read more about Creative commons licenses: https://creativecommons.org/licenses/

#### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

#### LUND UNIVERSITY

**PO Box 117** 221 00 Lund +46 46-222 00 00

YLVA GÅRDINGERS DEPARTMENT OF TRANSLATIONAL MEDICINE | FACULTY OF MEDICINE | LUND UNIVERSITY



Ylva Gårdinger



#### DOCTORAL DISSERTATION

by due permission of the Faculty of Medicine, Lund University, Sweden. To be defended in room 2005/2007, Carl-Bertil Laurells gata 9, Skåne University Hospital, Malmö on the 30th of May 2024 at 09.00 AM

> *Faculty opponent* Professor Jan Engvall, Linköping University

#### Organization: LUND UNIVERSITY

#### Document name: Doctoral dissertation

#### Author: Ylva Gårdinger

#### Date of issue 2024-05-30

#### Sponsoring organization:

#### Title and subtitle: Effects of food intake on echocardiographic measurements

#### Abstract:

Echocardiography is a commonly used imaging modality of the heart, both in daily clinical practice and scientific studies. Digestion of food is known to affect hemodynamics. The aim of this thesis was to evaluate if and how food intake affects various systolic and diastolic echocardiographic measurements. The cardiovascular system changes with advancing age, and we have therefore examined first a young and then an older population and compared results.

In papers I - III we investigated 23 healthy subjects 25.6±4.5 years of age. They were examined with echocardiography after overnight fasting and then 30 and 110 minutes after eating a standardized meal.

Meridional and circumferential left ventricular end-systolic wall stress was shown to decrease significantly (P<0.001) 30 minutes after the meal in paper I and was not back to baseline after 110 minutes.

In paper II, systolic tissue Doppler velocities (s') were measured with pulsed tissue Doppler at six sites in the left ventricle and one site in the right ventricle. Thirty minutes postprandially there was a significant increase in velocity at all sites except one (p<0.05). Some measurements were still increased at 110 minutes after the meal.

Myocardial performance index (MPI) of the left ventricle was examined in paper III and found to significantly decrease (p<0.001) 30 minutes after food intake. No significant change remained at 110 minutes postprandially.

In paper IV, 30 healthy seniors, 67.5±1.2 years of age, were examined with echocardiography after overnight fasting, and then at 30, 90 and 180 minutes after a standardized meal. Many echocardiographic measurements were evaluated, reflecting systolic as well as diastolic function. At 30 minutes several significant changes (p<0.05) were seen, ranging between 3-45% compared to baseline. None of the changes remained significant 180 minutes postprandially.

The thesis shows that food intake affects several echocardiographic parameters, reflecting both systolic and diastolic function. With a few exceptions, the findings are less pronounced in the older population. The findings are not of consequence for echocardiographic examinations in clinical practice but suggest that food intake should be taken into consideration in studies, especially when the investigated population is small.

**Key words:** Echocardiography, diastolic function, systolic function, Doppler, left ventricular wall stress, myocardial performance index, food intake

Supplementary bibliographical information

Language: English	ISSN and key title: 1652-8220		
ISBN: 978-91-8021-572-5			
Recipient's notes	Number of pages: 65		
Price	Security classification		

I, the undersigned, being the copyright owner of the abstract of the above-mentioned dissertation, hereby grant to all reference sources permission to publish and disseminate the abstract of the above-mentioned dissertation.

Signature

Ylva Gårdinger



Coverphoto by Ylva Gårdinger Heart shaped stones found on Öland Copyright pp 1-65 Ylva Gårdinger

Paper 1 © Open access Paper 2 © John Wiley & Sons Paper 3 © Open access Paper 4 © John Wiley & Sons

Faculty of Medicine Department of Translational Medicine

ISBN 978-91-8021-572-5 ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University Lund 2024



Media-Tryck is a Nordic Swan Ecolabel certified provider of printed material. Read more about our environmental work at www.mediatryck.lu.se

MADE IN SWEDEN

# Table of Contents

List of papers	9
Populärvetenskaplig sammanfattning	10
List of abbreviations	12
Introduction	14
Food intake	14
The Digestive Tract	14
Meal Composition and Postprandial Changes	15
The Heart	16
Age-related changes of the cardiovascular system	22
Hemodynamic consequences of food intake	24
Different methods to assess cardiac function	25
Echocardiography	25
Cardiac magnetic resonance imaging	26
Cardiovascular Computed Tomography	26
Nuclear cardiology	27
Objectives	28
Objectives Material and methods	28 29
Objectives Material and methods Study population	<b>28</b> <b>29</b> 29
Objectives Material and methods Study population Procedures	<b>28</b> <b>29</b> 29 29
Objectives Material and methods Study population Procedures Echocardiography	<b>28</b> <b>29</b> 29 29 30
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis	<b>28</b> <b>29</b> 29 30 32
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses	<b>28</b> <b>29</b> 29 30 32 33
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses Results	28 29 29 30 32 33 34
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses Results Papers I-III	28 29 29 30 32 33 34 34
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses Results Papers I-III Paper I	28 29 29 30 32 33 34 34 35
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses Results Papers I-III Paper I Paper II	28 29 29 30 32 33 34 34 35 38
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses Results Papers I-III Paper I Paper II Paper III.	28 29 29 30 32 33 34 34 35 38 39
Objectives Material and methods Study population Procedures Echocardiography Overview of analyzed echocardiographic parameters in this thesis Statistical analyses Results Papers I-III Paper I Paper II Paper III Paper IV	28 29 29 30 32 33 34 34 34 35 38 39 40

Discussion	43
Baseline findings	44
Changes 30 minutes after food intake	44
Changes 90, 110, and 180 minutes after food intake	47
Food intake and echocardiography	47
Limitations	49
Conclusions	51
Future perspectives	52
Errata	54
Paper I	54
Paper II	54
Paper IV	55
Acknowledgements	56
References	57

# List of papers

This thesis is based on the following papers, reprinted with permission from the publishers, and referred to by their Roman numerals in the text:

- I. **Gårdinger Y**, Bjorgell O, Hlebowicz J, Dencker M. Effect of food intake on left ventricular wall stress. Cardiovascular Ultrasound. 2014:12:2.
- II. Dieden A, Gårdinger Y, Bjorgell O, Hlebowicz J, Dencker M. Effect of food intake on systolic tissue Doppler measurements. Clin Physiol Funct Imaging. 2016:36:396-400.
- III. Gårdinger Y, Dieden A, Hlebowicz J, Bjorgell O, Dencker M. Effect of food intake on myocardial performance index. Cardiovascular Ultrasound. 2017:15:10.
- IV. Gårdinger Y, Malmgren, A, Hlebowicz J, Dencker M. Effect of food intake on echocardiographic measurements in healthy elderly. Echocardiography. 2022:39:811-818.

Scientific contributions that are not included in the dissertation:

Dencker M, **Gårdinger Y**, Bjorgell O, Hlebowicz J. Effect of food intake on 92 biomarkers for cardiovascular disease. PLoS One 2017:e0178656.

Dencker M, **Gårdinger Y**, Bjorgell O, Hlebowicz J. Effect of food intake on biomarkers for cardiovascular disease with the Proseek Multiplex CVD II kit. Genetics and Molecular Research 2018:17:1:16039884.

# Populärvetenskaplig sammanfattning

Hjärtat är en fantastisk muskelpump, som förser hela kroppen med blod. Det finns fyra rum i hjärtat - två förmak och två kammare - som mynnar i klaffar, vilka kan öppnas och stängas. Den högra sidan tar emot syrefattigt blod via förmaket, och höger kammare pumpar det sedan vidare till lungorna för att syresättas. Därefter kommer blodet tillbaka till vänster sida via vänster förmak, och den vänstra kammaren pumpar ut det i kroppen. Detta sker dag och natt, om och om igen. Man kan dela in varje hjärtslag i två faser – diastole, när kamrarnas muskelfibrer slappnar av och kammaren fylls med blod och systole, när muskelfibrerna dras samman och blodet pumpas ut. De har båda en viktig del i hjärtats funktion, och kan påverkas av många olika faktorer och sjukdomar. Framför allt den diastoliska fasen påverkas även av normalt åldrande.

Ett ofta använt sätt att studera hjärtats funktion är ultraljud, så kallad ekokardiografi. Man tittar genom bröstkorgsväggen med hjälp av en ultraljudsapparat och får en bild av hjärtat, där man bland annat kan se hur väggar och klaffar rör sig. Det är smärtfritt och ofarligt och används rutinmässigt på sjukhusen både för att till exempel snabbt skatta hur bra ett hjärta pumpar och för mer detaljerade undersökningar av hjärtfunktionen.

När vi äter mat påverkas blodflödet i kroppen, och mer blod går till magsäcken och tarmarna. Man har sett att hjärtat pumpar ut mer blod varje minut, både genom att pumpa snabbare och genom att öka mängden blod i varje hjärtslag. Vi vet inte exakt hur detta går till, men man har visat att bland annat blodsockernivån samt insulin och flera andra signalsubstanser i blodet kan påverka hjärtat och blodkärlen.

I forskningsstudier där ekokardiografi används brukar man inte nämna något om huruvida undersökningen är gjord på en fastande person, eller någon som nyss ätit.

Den här avhandlingens syfte är att ta reda på om matintag påverkar hjärtats funktion på sätt som kan mätas med ultraljud. Eftersom hjärtat, liksom resten av kroppen, naturligt förändras en del med åldern har vi undersökt både unga och äldre personer för att se om resultaten skiljer sig åt.

För att ta reda på mer om hur hjärtfunktionen påverkas när vi äter, har vi i avhandlingens olika delarbeten, med hjälp av ultraljud, tittat närmare på vad som händer med en mängd olika parametrar, som speglar hjärtats funktion, efter att deltagarna ätit en portion gröt. Alla deltagare är först undersökta i vila, efter att ha fastat över natten, och därefter vid olika bestämda tidpunkter efter måltiden. Mellan undersökningarna har deltagarna vilat på en brits.

I de första tre delarbetena undersökte vi 23 unga, friska män och kvinnor (20-30 år), först fastande och därefter 30 respektive 110 minuter efter måltiden.

I delarbete I undersökte vi vänsterkammarens funktion genom att räkna ut något som kallas wallstress och fann att den påverkades av matintag. I delarbete II använde vi en form av ultraljud som kallas vävnadsdoppler och fann att höger och vänster kammares systoliska funktion påverkades av måltiden. I delarbete III fann vi att ett mått på vänster kammares funktion som benämns myocardial performance index (MPI) påverkades av matintag.

I delarbete **IV** undersökte vi 30 friska, äldre män och kvinnor (65-70 år), först fastande och därefter 30, 90 och 180 minuter efter måltid. Vi tittade på ett stort antal mått som speglar hjärtats systoliska och diastoliska funktion och fann att de flesta påverkades av matintag. Störst påverkan fann vi på wallstress och MPI, som till stor del kvarstod efter 90 minuter. Efter 180 minuter var nästan alla mått tillbaka vid utgångsvärdena.

När man jämförde de yngre och äldre deltagarna, fanns många likheter - men också skillnader - både i fastande utgångångsvärden och i förändringarna som sågs efter matintag.

Sammanfattningsvis har vi funnit att matintag påverkar ett flertal mått som undersöks med ultraljud och speglar hjärtats funktion. Det är knappast något som har betydelse för de vardagliga undersökningarna, som görs i sjukvården, men något som kan vara viktigt att beakta i forskningssammanhang, där skillnaderna kan ha betydelse för slutsatserna som dras, särskilt i studier där endast ett mindre antal personer ingår.

# List of abbreviations

А	Late diastolic mitral flow velocity				
a´	Pulsed tissue Doppler late mitral annular diastolic				
	velocities				
BMI	Body mass index				
BP	Blood pressure				
BPM	Beats per minute				
BSA	Body surface area				
CCK	Cholecystokinin				
cESS	Circumferential end-systolic wall stress				
CI	Cardiac index				
CMR	Cardiac magnetic resonance imaging				
CO	Left ventricular cardiac output				
CCT	Cardiac computed tomography				
D	Pulmonary vein peak velocity in diastole				
DBP	Diastolic blood pressure				
DT	Deceleration time of the E-wave				
E	Early diastolic mitral flow velocity				
e′	Pulsed tissue Doppler early mitral annular diastolic				
	velocities				
EDV	End-diastolic volume				
ENS	Enteric nervous system				
ESS	Meridional end-systolic wall stress				
ESV	End-systolic volume				
ET	Ejection time				
FT	Feature tracking				
GIP	Glucose-dependent insulinotropic polypeptide				
GLP-1	Glucagon-like peptide 1				
GLP-1RA	GLP receptor agonist				
GLS	Global longitudinal strain				
HR	Heart rate				
ICT	Isovolumetric contraction time				
IRT	Isovolumetric relaxation time				
IVS	Interventricular septum thickness in diastole				
L	Liter				
LA	Left atrial end-systolic diameter				

LVEDP	Left ventricular end-diastolic pressure		
LVEF	Left ventricular ejection fraction		
LVIDd	Left ventricular inner diameter in end-diastole		
LVIDs	Left ventricular inner diameter in end-systole		
LVM	Left ventricular mass		
LVOT	Left ventricular outflow tract		
LVOT VTI	Left ventricular outflow velocity-time integral		
MAPSE	Mitral annular plane systolic excursion		
MMC	Migrating motor complex		
MPI	Myocardial performance index		
0'	wall stress		
Р	Pressure		
PET	Positron emission tomography		
PWTd	Posterior wall thickness in diastole		
PWTs	Posterior wall thickness in systole		
R	Radius of a cylinder		
S	Pulmonary vein peak velocity in systole		
s′	Pulsed tissue Doppler peak systolic velocities		
s' right ventricle	Pulsed tissue Doppler peak systolic tricuspid annular		
	velocity		
	at the free wall		
SBP	Systolic blood pressure		
SMA	Superior mesenteric artery		
SPLV	Left ventricular systolic pressure		
SPECT	Single-photon emission computed tomography		
SRLV	Left ventricular systolic radius		
SV	Left ventricular stroke volume		
Т	Tension		
TAPSE	Tricuspid annular plane systolic excursion		
TDI	Tissue Doppler Imaging		
TTE	Transthoracic echocardiography		
W	Wall-thickness		

# Introduction

"Life is a combination of magic and pasta" the great Italian film director Federico Fellini once supposedly stated, and the quote, "Everything you see, I owe to spaghetti," is said to come from Sophia Loren. Regardless of whether you are a pasta loving Italian or prefer other cuisine, food intake is a part of everyday life: It is a source of nutrition, pleasure, comfort, or a little of each. What we perhaps do not consider while we munch on our sandwich or chew our Sunday steak is that the digestion of food has hemodynamic effects.

### Food intake

Since this thesis focuses on hemodynamic postprandial changes, we will begin with a description of how food travels through the digestive tract and how nerves, hormones, and blood glucose are affected by the food we ingest.

### The Digestive Tract

The stomach comprises distinct sections: the fundus (proximal region) and the corpus with the antrum (distal region). Its boundaries are demarcated by the lower esophageal sphincter and the pylorus. Internally, the stomach wall consists of the mucosa, housing mucous cells; parietal cells responsible for hydrochloric acid and intrinsic factor production; and chief cells generating pepsinogen. Enclosed within the submucosa lies the submucosal (Meissner's) plexus, followed by the muscular layer composed of circular and longitudinal muscles. Additionally, the proximal region harbors oblique muscles that thicken approaching the pylorus. The myenteric (Auerbach's) plexus lies between the longitudinal and circular muscle layers, and the outermost layer, the serosa, connects with the omentum [1].

The stomach receives extrinsic autonomic innervation bifurcated into parasympathetic and sympathetic systems [1]. Parasympathetic signals originate from the vagus nerve, which is housed in the brainstem's nucleus ambiguous, nucleus dorsalis, and tractus solitarius [2]. Comprising 20% efferent fibers and 80% afferent sensory fibers, the vagus nerve relays information to the brain [3]. Afferent

fibers in the gastric mucosa, muscularis, and serosa respond to stretching, motility, and chemical stimuli [4]. Meanwhile, efferent fibers exert both excitatory and inhibitory influences on gastric motor function [4]. Sympathetic innervation emanates from the thoracolumbar region of the spinal cord [1].

The stomach also houses intrinsic innervation provided by the enteric nervous system (ENS). This system encompasses the myenteric plexus, between the circular and longitudinal muscle layers, and the submucosal plexus within the stomach wall's submucosa. Within the ENS, a variety of neurotransmitters and hormones—both stimulatory (e.g., acetylcholine, serotonin, histamine, cholecystokinin, angiotensin, motilin, and gastrin) and inhibitory (e.g., dopamine, noradrenaline, glucagon, vasoactive intestinal polypeptide, somatostatin, and enkephalin)—have been identified. These substances can be released through neurocrine, paracrine, and endocrine pathways [1].

Primarily, the stomach's role involves mechanically and chemically breaking down ingested food into chyme and delivering it to the duodenum at a suitable pace. Postprandially, the proximal stomach undergoes a 20-second receptive relaxation upon food intake, followed by adaptive relaxation as food enters. The vagus nerve's sensory and motor fibers mediate postprandial gastric motility, regulating stomach pressure to prevent food reflux into the esophagus. Subsequent contractions begin in the distal stomach after food intake, irregularly initially and then at a rate of 3 waves per minute, propelling food towards the duodenum. Coordinated peristaltic waves move from the antrum to the pylorus, facilitating the controlled passage of liquids and small particles [1].

During the fasting state, known as phase I, which lasts approximately 40 minutes, the stomach remains inactive. Phase II, which also lasts about 40 minutes, involves irregular and heightened peristaltic contractions in the stomach. Phase III represents the period when the stomach reaches its maximum contraction force and rate (three peristaltic waves per minute), which is sustained for about 10 minutes. Throughout this phase, the lower esophageal sphincter experiences peak pressure, and the pylorus remains open enabling the passage of larger food particles out of the stomach. Following this, the stomach reverts to phase I, initiating a 90-minute cycle known as the interdigestive migrating motor complex (MMC), which is regulated by the enteric nervous system [1].

### **Meal Composition and Postprandial Changes**

Gastric emptying varies depending on meal composition and type. Liquids depart the stomach rapidly while semi-solid and solid meals have a delayed linear departure. Factors such as food volume, osmolarity, chemical composition (e.g., amino acids, sugars, fats, and pH), and particle size influence the rate of gastric emptying. Hypertonic liquids empty slower than hypotonic ones. Particles smaller than 0.5-1.5 mm can pass through the pylorus while larger indigestible particles leave during Phase III of the MMC. Gastric emptying occurs at an approximate rate of 2 kcal per minute into the duodenum [1]. Additionally, gastric emptying rates are affected by meal volume, energy density [5], hypoglycemia [6-8], hyperglycemia [9-11], fluctuations in blood glucose levels [12], hyperinsulinemia [13, 14], body weight [15, 16], smoking [17, 18], gender [19-21], and various medications [1].

Lipids present in the small intestine prompt the secretion of cholecystokinin (CCK) from the mucosa located in the duodenum and jejunum [1]. CCK, in turn, stimulates postprandial bile secretion into the duodenum and acts as an inhibitor of postprandial gastric emptying [1, 22]. Concurrently, the gut peptide motilin, synthesized in the proximal small intestine, exhibits increased plasma concentration at the onset of phase II of the MMC. Its concentration peaks during phase III, subsequently promoting gastric emptying and showing associations with gall bladder contractions. Despite unclear stimuli for motilin release, it has been proposed that duodenal bile might play a role in its secretion [1, 23].

Various gastrointestinal hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are secreted by the K- and L-cells present in the intestinal wall [24]. GLP-1 inhibits gastric emptying, leading to reduced insulin and glucagon levels post-meal, and thereby resulting in lower blood glucose levels [25-30].

In the fasting state, blood glucose regulation relies on glucagon secretion by the  $\alpha$ cells situated in the islets of Langerhans within the pancreas. This action triggers the release of glucose stored in the liver, primarily from the breakdown of glycogen via glycogenolysis. Basal insulin secretion during fasting helps to moderate excessive glycogenolysis. Extended fasting periods stimulate gluconeogenesis, which involves the breakdown of amino acids, glycerol, and lactate to release glucose from the liver [24].

### The Heart

The heart has four rooms, divided into two atria (left and right) and two ventricles (also left and right). The blood flow through the atria and ventricles are regulated by heart valves: two atrioventricular (A-V) valves (the tricuspid and mitral valves) and the seminlunar valves (the aortic and pulmonary valves). Venous blood, low on oxygen, from the lower extremities enters the right atrium from vena cava inferior and from the upper extremities through vena cava superior. Blood flow between the right atrium and right ventricle is regulated by the tricuspid valve. The right ventricle pumps the blood to the pulmonary arteries and then to the lungs for oxygenation,

and this is controlled by the pulmonary valve. The oxygenated blood then returns from the lungs and enters the left atrium through four pulmonary veins. Thereafter, the blood enters the left ventricle through the mitral valve. The left ventricle then pumps the blood through the aortic valve to the peripheral organs for oxygenation [31, 32]. Figure 1 provides an overview of the anatomy of the heart.



**Figure 1.** A schematic overview of the anatomy of the heart. Adopted from Wikipedia Commons (https://commons.wikimedia.org/wiki/File:Heart\_diagram-en.svg) Licensed under a Creative Commons Attribution license (CC BY-SA 3.0 DEED Attribution – ShareAlike 3.0 Unported).

Each cardiac cycle is initiated by the sinus node and consists of diastole—a period of relaxation when the heart fills with blood, followed by systole, a period of contraction when blood is pumped into the aorta and pulmonary artery. In early diastole, the ventricles quickly fill with blood that has been pooled in the atria during systole (when the A-V valves are closed). This is the period of rapid filling. In late diastole, the atria contract and give a smaller additional inflow of blood, the period of late filling. When the ventricular contraction begins the pressure abruptly rises, and the A-V valves close. For a short while all valves are closed, and the ventricle is a closed room with constant volume while the muscle contracts. This is the period of isovolumetric contraction and the start of systole. When the ventricular pressure exceeds the arterial pressure, the aortic and pulmonary valves open and blood pours out of the ventricles. This is the period of ejection. When the ventricles relax, and pressure falls below that in the arteries, the semilunar valves close and the ventricles are once more closed rooms, there is a short period of isovolumetric relaxation, which marks the start of diastole. When the atrial pressure exceeds the ventricular pressure, the A-V valves open again, and a new cycle begins [31, 32]. The Wiggers diagram named after Dr. Carl J. Wiggers (1883 – 1963) is a commonly used way to depict the time relations between pressures, volumes, electrical activities and heart sounds during the cardiac cycle [33], and one version of it is displayed in Figure 2.



**Figure 2.** Wiggers diagram is an overview of the time relations between pressures, volumes, electrical activities and heart sounds during the cardiac cycle. From Wikimedia Commons revised by Dr. Chang (https://en.wikipedia.org/wiki/Wiggers\_diagram#/media/File:Wiggers\_Diagram\_2.svg) licensed under a Creative Commons Attribution license (CC BY-SA 4.0 DEED Attribution-ShareAlike 4.0 International).

Cardiac Output (CO) is the amount of blood the heart pumps into the aorta each minute, and it varies with activity level. It is the product of the heart rate (HR) and the stroke volume (SV). The SV is the volume of blood pumped from the ventricle

each beat and is mainly influenced by preload, afterload, and contractility. The average cardiac output for an adult at rest is about 5 l/min. [31, 32].

Preload has been described with some variability in textbooks. Based on the Law of Laplace (a physics law stating that the wall tension (T) of a thin-walled, hollow cylinder is proportional to the pressure of its contents (P) and its radius (R): T=PR/2)) it can be explained as the ventricular wall tension at the end of diastole. Since the left ventricle is a thick-walled structure, we can also describe preload as end-diastolic wall stress and adjust for myocardial thickness as follows:  $\sigma$ =PR/2w. Wall stress ( $\sigma$ ) is thus related to T and wall thickness (w) as  $\sigma$ =T/w. So, preload is closely related, but not equal as sometimes said, to left ventricular end-diastolic filling pressure (LVEDP) or end-diastolic volume. With this reasoning, everything that affects the diastolic pressure, the radius, or the wall-thickness contributes to preload. Thus, important factors are, for example, circulating blood volume and changes in venous tone (Figure 3) [34].

Afterload has also been described in various ways in textbooks. Based on Laplace's equation, it can be described as the tension (T) or wall stress ( $\sigma$ ), when adjusted for wall thickness, that the myocardium develops during the systolic ejection. It is calculated from the end-systolic pressure and radius of the left ventricle. It is often also described as the resistance, or pressure, that the ventricles must overcome to eject the blood volumes. So,all factors that contribute to total myocardial tension (or wall stress) during systolic ejection affect afterload. Arterial pressure and total peripheral resistance are key factors, but while they are important, they do not represent the whole truth (Figure 4)[34].

From the reasoning above we see that the simplified equation for explaining left ventricular wall stress is (SPLV)(SRLV)/2wLV where SPLV is left ventricular systolic pressure, SRLV left ventricular systolic radius and wLV is the wall thickness of the left ventricle. There are, however, more detailed equations used in studies for meridional (ESS) and circumferential (cESS) end-systolic wall stress, which can be found under Materials and Methods.



**Figure 3**. Adapted from Norton J.M. Advances in Physiology Education 2001:25:53–61. Flow diagram of the various cardiovascular factors that contribute to preload, and, therefore, end-diastolic myocardial passive wall stress. The reasoning is based on the law of LaPlace with the parameters chamber radius, chamber pressure, and wall thickness.



**Figure 4.** Adapted from Norton J.M. Advances in Physiology Education 2001:25:53–61. Flow diagram of the various cardiovascular factors that contribute to afterload, and, therefore, also myocardial wall tension/wall stress during systole, based on the law of LaPlace with the parameters chamber radius, chamber pressure, and wall thickness.

The heart is composed of specialized muscle cells, myocytes, sensitive to calcium ions [31, 32]. The left ventricle can be described as prolate ellipsoid in shape [35]. The muscle fibres have various orientations with a more longitudinal, helical arrangement in the inner and outer layer of the left ventricle (subendocardial and subepicardial) and a more circumferential orientation in the midwall [36]. The complex geometry of myofibers forms a right-handed helix in the subendocardium and gradually changes to a left-handed helix in the subepicardium, and the left ventricle contracts with a wringing motion to generate ejection [35]. The right ventricle differs in several ways both anatomically and functionally from the left ventricle. The free wall is thinner and the volume larger although the mass is smaller. In addition, the structure of the wall with different layers of fibre orientation differs. Although the myofibers form helical arrangements also in the right ventricle, there is normally no defined midwall layer with more circumferential oriented fibres, as in the left ventricle. The subepicardial layer of the right ventricle has instead more circumferential oriented myofibers, which gives an inward movement of the free wall during right ventricle ejection-the "bellows effect." The helical, oblique subendocardial fibres are responsible for shortening of the longitudinal axis accounting for the larger part of the ejection fraction. A third pump mechanism comes from the effect of left ventricular contraction on the intraventricular septum and free wall [37-40]. The anatomical differences between the left and right ventricles have consequences for the different echocardiography measurements performed in this thesis and will be addressed later. In addition, it has been suggested that longitudinal function accounts for 60% of SV for the left ventricle, whereas radial motion generates 40% of the SV. In the right ventricle, long axis function is more important and accounts for 80% of the SV and radial function 20% of the SV [41].

### Age-related changes of the cardiovascular system

Aging affects the cardiovascular system with structural as well as functional changes. There is a vascular thickening and stiffening where loss of arterial compliance contributes to a rising systolic blood pressure and increase in afterload. The myocardium also stiffens with increased left ventricular wall thickness, which is more pronounced in the interventricular septum than the free wall [42-45]. Both the end-systolic (ESV) and end-diastolic left ventricular volumes (EDV) decreases with age, and the left ventricle gets more spherical in shape as the end-diastolic length shortens [46-48]. Autopsy studies have shown that there is an age-related attrition of myocytes while the remaining myocytes hypertrophies [49], which together with a deposition of connective tissue from fibroblasts, can lead to the increase seen in ventricle wall thickness and stiffening

[45, 46]. In more recent years, 3D-echocardiography and cardiac magnetic resonance has facilitated a more accurate assessment of the anatomy of the right ventricle, and the smaller end volumes and cavity dimensions seen in the left ventricle with advancing age applies also to the right ventricle [50, 51]. Left atrial volume has been shown to increase with advancing age [52] while enlargement has not been established as normal aging for the right atrium [53].

Studies report divergent results regarding systolic function of the left ventricle assessed by left ventricular ejection fraction (LVEF). Although some studies have found that systolic function increases with advancing age, several studies have not shown any significant change in LVEF, and the overall left ventricular systolic function at rest does not appear to be affected in healthy aging [36, 45, 46]. With age, however, comes a decreasing tolerance of exercise with reduced cardiac output mainly due to impaired heart rate acceleration. The SV is mostly maintained as left ventricular-end diastolic volume increases [45, 46]. Another measurement of systolic function, global longitudinal strain (GLS), has been found to show lower normal values in elderly compared to younger individuals [54] although this method is technically challenging with different reported normal values between different vendors.

Age is well-known to affect the diastolic function of the left ventricle, and it is sometimes hard to draw the line between dysfunction and normal aging. The diastolic filling changes as the left ventricle grows stiffer and the myocardial relaxation is prolonged. The left ventricular end-diastolic pressure increases and the early diastolic phase with rapid, passive filling decreases, which makes the atrial contraction phase during the period of late filling more important [43, 45, 46, 55]. Hence, echocardiography with pulsed Doppler shows a decrease in early transmitral flow velocity (E) with advancing age, as well as an increase in late transmitral flow velocity (A) and a lower E/A ratio and a prolongation of E-wave deceleration time. In addition, there is an increase in the systolic flow velocity (S) in the pulmonary venous flow, a decrease in diastolic flow velocity (D), and an increase in their ratio (S/D). Tissue Doppler early mitral annular velocity (e') decreases with advancing age probably due to the slower relaxation, while the ratio of mitral E/e` increases [46, 56]. Aging of the heart also is associated with degenerative changes in the valvular apparatus with calcifications and annular dilation, as well as of the cardiac conduction system [43, 45].

# Hemodynamic consequences of food intake

Intake and digestion of food leads to several hemodynamic changes. More blood is needed in the splanchnic organs, and the blood flow in the superior mesenteric artery (SMA) increases while the total systemic resistance falls. The CO also increases, and the changes develop gradually to peak at 30-60 minutes postprandially [57-59]. The increase in CO is due both to an increase in SV and HR [60, 61]. The diastolic blood pressure decreases while the systolic blood pressure is basically the same [57]. A larger meal gives a bigger and longer lasting increase in CO than a smaller one [62], and the postprandial changes in SMA flow and cardiac output are seen for meals containing carbohydrates as well as fat or protein [58]. A redistribution of flow also contributes to meeting the increased need of blood to the splanchnic organs in addition to the increase in CO [58].

The exact mechanisms behind the cardiovascular changes are not known. The heart is innervated by the autonomic nervous system, which has two interacting systems: the parasympathetic nervous system controlled by the vagus nerve and the sympathetic system. Sympathetic stimulation increases the heart rate (chronotropic), contractility (inotropic), and conduction velocities while parasympathetic stimulation acts as a brake with opposite effects [63]. Some hemodynamic changes seen postprandially could be mediated by the autonomic nervous system. However, an increase in cardiac output matching the increased postprandial blood flow in SMA also has been shown in heart transplants (thus with denervated hearts), indicating some sort of humoral connection [64, 65]. Cardiovascular postprandial changes also may be influenced by alterations in glucose and insulin levels, as well as hormonal signals. Fasting levels of glucose in blood is normally < 6.1 mmol/L. When we eat, the levels of glucose normally rise within 15 minutes and can increase about 1-2 mmol/L in healthy individuals, and when glucose increases, insulin is secreted from the pancreas. Insulin is a vasodilator that stimulates production of nitric oxide from the endothelium. It increases blood flow and augments glucose disposal in skeletal muscle [66]. It has also positive inotropic and chronotropic effects of the heart [67] and increases uptake of glucose in the myocardium. Grehlin is a multifaceted hormone produced in the ventricle. It has multiple metabolic effects, among which are stimulating secretion of the growth hormone and enhancing appetite. It has a glucoregulatory action and also has been shown to improve left ventricular dysfunction [68]. Another hormone of interest is the incretin GLP-1, and its receptor agonist (GLP-1RA) which is used as a type 2 diabetes drug.

### Different methods to assess cardiac function

### **Echocardiography**

There are many different imaging methods available to evaluate cardiac size and function. Echocardiography is an imaging of the heart using ultrasound and is often the first modality of choice to evaluate cardiac function. It can be used to study many aspects of cardiac function, e.g., quantification of chamber size, assessment of both systolic and diastolic function, structural and functional measurements of cardiac valves, and examination of the proximal aorta [69, 70].

Inge Edler and Hellmuth Hertz from Lund, Sweden, presented M-mode in 1953, the first version of echocardiography [71]. Echocardiography has since developed into a diagnostic tool that is highly utilized, widely available, non-invasive, costeffective, and without known risks. It is used every day in clinical practice for rapid evaluation of critically ill patients [72-74] as well as for thorough investigations of, for example, chamber size, valve function, and myocardial contractility [69, 75]. A detailed transthoracic echocardiographic examination involves imaging the heart from various views. The transducer is used in different positions (parasternal, apical, subcostal, parasternal) and with different orientation of the tomographic plane through the heart (long axis, short axis, four, three, two chamber) [76]. There are various imaging ultrasound modes used to acquire different data. M-mode, as mentioned above, is a single beam scan with high time-resolution (>100 frames per second), which is useful in assessing motion in, for example, valves and chamber walls. Two applications of the M-mode technique are measurement of the mitral annular plane systolic excursion toward the apex (MAPSE) and the tricuspid annular plane systolic excursion also toward the apex (TAPSE). MAPSE is usually measured at the septal and lateral walls of the left ventricle and sometimes also measured at the inferior and anterior walls. TAPSE is measured at the right ventricular free wall. Both measurements reflect the longitudinal function of the respective ventricles. Two-dimensional imaging gives anatomical information about chambers, valves, and great vessels as well as an assessment of ventricular movement and function. Pulsed wave Doppler and continuous Doppler investigates the direction and velocity of blood flow, while tissue Doppler is used for myocardial movement, which is much slower than blood [75, 76]. Pulsed Doppler is used for hemodynamic assessment by calculation of CO and SV. It is also an important measurement tool when evaluating the left ventricular diastolic function. Speckle tracking can be used to assess the global strain, i.e., the deformation of the myocardium that occurs during the cardiac cycle [77]. In addition, 3-dimensional (3D) echocardiography has emerged in recent decades making it possible to overcome the shortcomings of the geometric assumptions of 2-dimensional calculations [78]. It has, however, lower spatial and temporal resolutions, making it less suitable for studying different rapid cardiac aspects. In the past two decades, transpulmonary contrast echocardiography has emerged as a tool to provide better visualization of endocardial borders of the left ventricular walls, and for the assessment of intra cardiac structures (e.g., thrombi, tumors, and heart muscle disorders as non-compaction) [79, 80]. In addition, the use of contrast on 3D echocardiography results in improved accuracy for left ventricular ejection fraction and left ventricular volume measurements [81]. Contrast also has been shown to increase the reproducibility of these measurements [81, 82]. However, it also greatly enhances Doppler signals, which become difficult to measure. Echocardiography can provide much clinical data and is widely used in various studies [83] where it may monitor more subtle findings such as the prognostic value of MPI in patients with atrial fibrillation [84] or the effect of a medical treatment in patients with heart failure [85, 86]. In addition, there are numerous established and emerging measurements within echocardiography [83, 87].

There are, however, other methods to evaluate cardiac size and function. They all have one obvious factor in common: they all require heavy machines and are, therefore, not possible to use for bedside examinations.

### Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) is the gold standard for measuring ventricular and atrial volumes and function. CMR imaging has improved significantly over the past decades and is now such an important technique for evaluating cardiac disease that it is included in numerous guidelines by the European Society of Cardiology [88]. CMR combines excellent image quality with good temporal and spatial resolution and it is free of ionizing radiation. The technique has the advantage of being three-dimensional, and contrary to echocardiography, independent of acoustic windows. With CMR, viability, perfusion, and tissue characterization studies are also possible [89]. Potential challenges are irregular heart rhythm, claustrophobia, and the presence of metallic foreign material. Although studies with higher frame rates have been performed, the frame rates for cine-images are often between 20-30 frames per second compared to echocardiography m-mode and Doppler that usually has >100 frames per second, which makes it difficult to study rapid cardiac mechanical events [90].

### **Cardiovascular Computed Tomography**

Cardiac Computed Tomography (CCT) was introduced in the late 1990s and has since been a fast-evolving technique that provides information of cardiac and coronary anatomy. Its most established application is the evaluation of coronary artery disease with calcium scoring of the coronary arteries and non-invasive coronary angiography (CCTA) [25, 91-93], and it is a first-line diagnostic test for

patients with stable chest pain. In the acute setting, it is used primarily for patients with low-to-intermediate likelihood of coronary artery disease. Still, there are also many other fields where it is used to evaluate the coronary arteries, and it can detect discrete non-calcified plaques as well as significant stenosis. Apart from these primary applications, CCT can give reliable measurements of cardiac chamber size, left ventricular wall thickness, and both global and regional function by retrospective gating [94]. Myocardial perfusion imaging by CT and CT-derived fractional flow reserve (FFRct) are two other developing fields of study [92, 95]. The downsides are significant radiation exposure and iodine contrast. Good image quality is essential for a correct interpretation, and some factors can be problematic. Extensive coronary calcifications and significant obesity can hamper image quality, and an even and slow heart rhythm is desirable. Beta-blockers lower the heart rate to ideally less than 60-65 beats per minute, and nitroglycerin is used to dilate the coronary arteries [25, 93].

#### Nuclear cardiology

In nuclear cardiac imaging, there is single photon emission computed tomography (SPECT), cardiac positron emission tomography (PET), and equilibrium radionuclide ventriculography (ERNV), which is also called multigated angiography (MUGA) or radionuclide gated equilibrium radionuclide angiocardiography (ERNA). All have the capacity to measure cardiac size and function [96-101]. All nuclear techniques are based on injecting different radiopharmaceuticals and detecting their distribution. When ECG gating is applied, left ventricular volumes and function can be measured [96, 99]. ERNA is a wellvalidated, robust, and reproducible method to measure right and left ventricular global function, left ventricular volumes, and left ventricular regional and diastolic function [98, 101]. With regards to SPECT, it is primarily used to detect relative stress-induced regional myocardial perfusion defects in a qualitative or semiquantitative way. Left ventricular systolic and diastolic volumes and LVEF are routinely calculated in clinical practice. SPECT data for these variables has been shown to have a good correlation on a group level, but significant differences can be found on an individual level [102]. PET can quantify myocardial blood flow noninvasively and measure the coronary flow reserve. It has historically been used for serial assessments in different clinical scenarios where left ventricular global function has been the primary measurement to monitor over time. The aforementioned nuclear methods have been shown to provide reliable information of left ventricular size and global function. Still, it is not suitable for studying specific mechanical aspects of cardiac function, especially those occuring within a short time-period. All nuclear modalities have the same shortcoming: significant radiation exposure [103, 104].

# Objectives

The specific objective of this thesis was to assess whether food intake affects different echocardiographic measurements in various age groups.

The more specific objectives of the papers were as follows:

- I. To investigate whether left ventricular wall stress is affected by food intake in healthy young subjects.
- II. To investigate whether left and right ventricular systolic tissue Doppler measurements are affected by food intake in healthy young subjects.
- III. To investigate whether myocardial performance index is affected by food intake in healthy young subjects.
- IV. To investigate whether food intake affects systolic and diastolic echocardiographic measurements in healthy seniors, and whether it differs from previous findings in a young population.

As mentioned, food intake is a natural part of the day. It affects hemodynamics with altered loading conditions as more blood flows to the gastrointestinal tract, cardiac output increases, and blood pressure decreases. We have an available, safe, widely used imaging modality, echocardiography, that can provide an abundance of data. That the heart is affected postprandially in ways that can be measured with echocardiography seems reasonable. Such findings have previously been reported in our younger study population [105]. In this thesis, therefore, we investigate whether food intake affects various echocardiographic variables, both in a younger and older population, since the cardiovascular system changes with increasing age [42, 43, 45-47].

# Material and methods

### Study population

In papers I-III, a convenience sample of 23 volunteers aged 25.6±4.5 years were study subjects (11 male and 12 female). They had no history or symptoms of cardiovascular or any other chronic diseases and were not using any cardiovascular medications. Five participants were snuff users and one a smoker. All had sinus rhythm and an appropriate acoustic window. The study was approved by the regional ethical review board in Lund, Sweden (Dnr 2008/353). In paper IV, 30 subjects  $67.5\pm1.2$  years of age were recruited from the Swedish population register. Initially 300 people were randomly chosen and contacted by mail and invited to send a registration of interest. After telephone interviews and initial echocardiographic scans to ascertain an appropriate acoustic window and rule out unknown significant valvular disease (defined as mild stenosis or more than mild regurgitation) or other cardiac dysfunction, 15 females and 15 males were included. All were presumably healthy without any history of cardiovascular disease or medication, none were current smokers or snuff users, and all had sinus rhythm. All participants were informed in detail about the investigation, both verbally and in writing and gave a written consent. Some of the contacted people and subjects were found to have previously unknown valvular disease or untreated hypertension, of which they were informed and subsequently referred to a cardiologist. The study was approved by the regional ethical review board in Lund, Sweden (Dnr 2017/64).

### Procedures

Baseline examinations were performed in the morning after overnight fasting and 15 minutes of supine rest. Thereafter, the subjects consumed a standardized meal consisting of 300 g rice pudding (AXA Goda Gröten in papers I-III, and Felix Risgröt in paper IV since the former was discontinued). The caloric value of the meal was 330 kcal, of which 58-60% came from carbohydrates (both brands of pudding contained 48 g), 10-13% from protein (AXA 9 g and Felix 11g), and 27-32% from fat (AXA 12 g and Felix and 10 g). The subjects then reassumed a supine position. No smoking or use of snuff was allowed 8 h before or during the test. In

papers I-III the subjects went through echocardiographic examinations 30 and 110 minutes after the meal. In paper IV the echocardiographic examinations were performed 30, 90, and 180 minutes after food intake. Blood pressure (BP) and heart rate (HR) were measured before each exam, and between the exams the subject reassumed a supine position. In papers I-III, a manual sphygmomanometer with aneroid manometer and stethoscope was used to measure BP. Systolic and diastolic pressure (SBP and DBP) were identified by Korotkoff sounds phase I and V. In paper IV, a digital manometer (boso-medicus memory, BOSCH + SOHN, Jungingen, Germany) was used. Height and weight were measured before the examinations began, so that body mass index (BMI) and body surface area (BSA) could be calculated.

## Echocardiography

The echocardiographic examinations were performed transthoracically in left lateral position. All exams in papers I-III were made by one echocardiographer, and all exams in paper IV by another. Three separate cardiac cycles were stored digitally for each measurement, and the mean value for three measurements was used in the analyses. In papers I-III, a Philips Sonos 5500 (S3-transducer) (Philips, Andover, MA, USA) was used, and a single observer performed all measurements. In paper IV, a more modern machine was used, a Philips iE33 (S5-1 transducer) (Koninklijke Philips N.V, Philips Medical System, Amsterdam, The Netherlands), and a single observer performed each specific measurement.

A 2-D guided M-mode echocardiography from parasternal long-axis view was used to measure cardiac dimensions. M-mode also was used to assess mitral and tricuspidal annular plane systolic excursion (MAPSE and TAPSE). Left ventricular wall stress was calculated from M-mode tracings of cardiac dimensions. The formulas used are invasively validated [106, 107]. The formula for calculation of circumferential end-systolic wall stress (cESS):

$$cESS = \frac{(LVIDs/2)^2 x \{1 + (LVIDs/2 + PWTs)^2\}}{(LVIDs/2 + PWTs/2)^2\}}$$

**Abbreviations:** left ventricular internal dimension in systole (LVIDs), posterior wall thickness in systole (PWTs) and systolic blood pressure (SBP).

And for meridional end-systolic wall stress (ESS):

0.334 x SBP x LVIDs

ESS =

PWTs x {1+(PWTs/LVIDs)}

**Abbreviations:** left ventricular internal dimension in systole (LVIDs), posterior wall thickness in systole (PWTs) and systolic blood pressure (SBP).

From the apical four, three, and two-chamber view, pulsed wave Doppler parameters were acquired at the tip of the mitral leaflets. Pulmonary vein peak velocities were measured, as were left and right ventricle pulsed tissue Doppler peak velocities in systole and diastole. GLS was calculated with speckle tracking. The region of interest was traced along the left ventricular endocardium at end-diastole in the apical four-chamber, two-chamber and three-chamber view, respectively, and the software performed a propagated tracking. A manual correction was performed if needed. Left ventricular outflow velocity-time integral (LVOT VTI) and left ventricular outflow diameter were measured. Both SV and CO were calculated, and CO was indexed for BSA as cardiac index (CI). Myocardial performance index (MPI) was calculated from Doppler-derived measurements (Figure 5). To minimize respiratory changes, all tissue Doppler and pulsed wave Doppler measurements were performed at respiratory arrest after an end expiration.



Figure 5. Schematic figure of measurement and calculation of myocardial performance index. Myocardial performance index = (a-b/b).

# Overview of analyzed echocardiographic parameters in this thesis

**SV** - stroke volume (ml). The volume of blood pumped from the left ventricle with each heartbeat.

**CO** - cardiac output (L/min). The amount of blood the heart pumps into the aorta per minute. The product of stroke volume x heart rate.

CI - cardiac index. Cardiac output indexed for body surface area (BSA) (L/min/m<sup>2</sup>).

**LVOT VTI** - Left ventricular outflow velocity-time integral (cm). A measurement of blood flow out of the left ventricle used to calculate SV.

 ${\bf E}$  - peak of early diastolic mitral flow velocities (cm/s). Used to assess diastolic function of the left ventricle.

A - peak of late diastolic mitral flow velocities (cm/s). Used to assess diastolic function of the left ventricle.

E/A - ratio. Used to assess diastolic function of the left ventricle.

**DT** - deceleration time of the E-wave (msec). Used to assess diastolic function of the left ventricle.

 ${\bf S}$  - pulmonary vein peak velocities in systole (cm/s). Used to assess diastolic function of the left ventricle.

 ${\bf D}$  - pulmonary vein peak velocities in diastole (cm/s). Used to assess diastolic function of the left ventricle.

S/D - ratio. Used to assess diastolic function of the left ventricle.

e' - pulsed tissue Doppler peak early diastolic velocities (cm/s). Obtained at the septal and lateral wall of the mitral annulus. Used to assess diastolic function of the left ventricle.

 $\mathbf{a}'$  - pulsed tissue Doppler peak late diastolic velocities (cm/s). Obtained at the septal and lateral wall of the mitral annulus. Used to assess diastolic function of the left ventricle.

s' - pulsed tissue Doppler peak systolic velocities (cm/s). Obtained at the septal, lateral (and in paper II also inferior, anterior, inferolateral, and anteroseptal) wall of the mitral annulus. Used to assess systolic function of the left ventricle.

s' (right ventricle) - pulsed tissue Doppler peak systolic tricuspid annular velocity (cm/s). Obtained at the free wall. Used to assess systolic function of the right ventricle.

E/e'- ratio. Used to assess diastolic function.

**GLS** - global longitudinal strain (%). Here calculated with speckle tracking. A measurement of deformational change of (in this case) the left ventricle during systole. Used to assess the systolic function of the left ventricle.

**MAPSE** - mitral annular plane systolic excursion (mm). The displacement of the mitral annulus toward the apex during systole, obtained at the septal, lateral, inferior, and anterior walls. Used to assess systolic function of the left ventricle.

**TAPSE** - tricuspid annular plane systolic excursion (mm). The displacement of the tricuspid annulus toward the apex during systole obtained at right ventricle free wall. Used to assess systolic function of the right ventricle.

Left ventricular end-systolic wall stress - a measure of myocardial afterload (kdynes/cm<sup>2</sup>), the tension in the wall limiting the contraction of the left ventricle. It is calculated from the left ventricular inner diameter in end-systole (LVIDs) (mm/m<sup>2</sup>), the posterior wall thickness in end-systole (PWTs) (mm/m<sup>2</sup>), and systolic blood pressure. Meridional (ESS) and circumferential (cESS) end systolic wall stress are calculated separately. A bit simplified circumferential fiber shortening is limited by cESS while longitudinal fiber shortening is limited by ESS (formula in methods). Wall stress is dependent on the thickness of the myocardium, and, as described under preload/afterload in the introduction, it can be thought of as wall tension/wall thickness and calculated based on the law of Laplace (simplified wall stress:  $\sigma = PR/2w$ ). Hence, a hypertrophic wall can have a lower wall stress even if the blood pressure (contributing to a higher afterload) is high. A dilated ventricle has a higher wall stress. It is not a parameter used in clinical practice but has been studied in various research investigations.

**MPI** - myocardial performance index. Also known as Tei-index. Has been used as measure of total left (in this case) ventricular function, both diastolic and systolic. It too is a parameter mostly used in the context of research. Calculated as the sum of isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) divided by ejection time (ET) (Figure 5).

### Statistical analyses

In papers I-III, statistical analyses were performed using Statistica 7.1 (StatSoft Inc, Tulsa, OK, USA). In paper IV, the analyses were made using IBM SPSS Statistics 26. Data are presented as mean  $\pm$  standard deviation (SD) unless otherwise specified. Comparisons were made between baseline fasting values and values at 30 and 110 minutes after food intake (papers I-III) or 30, 90, and 120 minutes after food intake (papers I-III) or 30, 90, and 120 minutes after food intake (paper IV). Each variable was analysed for significance with Wilcoxon matched pairs test. A p-value of < 0.05 was considered statistically significant.

# Results

## Papers I-III

All participants had complete measurements in papers I and III. For paper II, some pulsed tissue Doppler measurements were not stored, and only 19 subjects were, therefore, included. None of the participants had any cardiac dysfunction. Descriptive characteristics of all the participants, including baseline echocardiographic cardiac dimensions, are summarized in Table 1.

Hemodynamically cardiac output with both stroke volume and heart rate increased significantly (p<0.001) 30 minutes after food intake. Diastolic blood pressure was lowered while the systolic pressure was not significantly altered.

Variable	
Sex (male/female)	11/12
Weight (kg)	68±11
Height (cm)	177±8
BMI (kg/m <sup>2</sup> )	21.7±2.2
BSA (m <sup>2</sup> )	1.8±0.2
LVIDd (mm/m <sup>2</sup> )	26.7±1.9
LVIDs (mm/m <sup>2</sup> )	17.7±1.9
IVSd (mm/m <sup>2</sup> )	5.1±0.4
PWTd (mm/m <sup>2</sup> )	5.0±0.4
LA (mm/m <sup>2</sup> )	18.2±1.9
LVM (g/m <sup>2</sup> )	87.6±18.1

Table 1: Subjects' anthropometric characteristics and cardiac dimensions (n=23). Values are mean  $\pm$  SD.

**Abbreviations:** Indexed for body surface area (BSA): left ventricular internal dimension in diastole (LVIDd), left ventricular internal dimension in systole (LVIDs), interventricular septum thickness in diastole (IVSd), posterior wall thickness in diastole (PWTd), left atrial end-systolic diameter (LA), and left ventricular mass (LVM).

## Paper I

Both meridional (ESS) and circumferential (cESS) left ventricular wall stress were significantly reduced (p<0.001) from fasting values 30 minutes after the meal and were still significantly reduced 110 minutes afterwards (Figure 6 and Figure 7). The decrease was, for both ESS and cESS, 32% compared to baseline values at 30 minutes and still 11% at 110 minutes. More specifically, the mean value for PWTs increased 30 minutes after food intake and was almost back at baseline at 100 minutes. The mean value for LVIDs, on the other hand, decreased at 30 minutes and was still a bit below baseline after 110 minutes. Systolic blood pressure was not significantly altered, while diastolic blood pressure (though not a part of the wall stress calculation) was significantly reduced. Though the equations differ, both meridional wall stress and circumferential wall stress are calculated from the systolic blood pressure, the inner dimension of the left ventricle in systole, and the thickness of the posterior wall in systole. Wall stress has been used as an index of myocardial afterload and has been shown to be affected by alterations in preload and afterload. With the altered loading conditions seen postprandially, it is not surprising that myocardial contractility changes. Table 2 provides an overview of the findings.

Variable	Fasting	30 minutes after food intake	110 minutes after food intake
ESS (kdynes/cm <sup>2</sup> )	65±16	44±12 ***	58±13*
cESS (kdynes/cm <sup>2</sup> )	98±24	67±18***	87±19**
LVIDs (mm)	32±3	28±4***	31±3*
PTWs (mm)	12.6±2.0	14.7±2.1***	13.2±1.7
SepWs (mm)	12.9±1.8	15.3±2.0***	13.7±1.9
Heart rate (bpm)	60±8	64±10**	60±10
Systolic BP (mm Hg)	103±9	102±10	102±9
Diastolic BP (mm Hg)	66±7	58±7***	63±6*

 Table 2 (n=23). Values are mean ± SD.

**Abbreviations:** Blood pressure (BP), meridional end-systolic wall stress (ESS), circumferential endsystolic wall stress (cESS), left ventricular inner diameter in systole (LVIDs), posterior wall thickness in systole (PWTs), and septal wall thickness in systole (SepWs). Please observe that values for cardiac size are reported in absolute values.

\*Indicates significant difference (P<0.05), compared to fasting values.

\*\*Indicates significant difference (P<0.01), compared to fasting values.

\*\*\*Indicates significant difference (P<0.001), compared to fasting values.



**Figure 6.** Meridional end-systolic wall stress (ESS) at baseline before the meal and 30 minutes and 110 minutes after the meal. ESS decreased significantly from  $65\pm16$  kdynes/cm<sup>2</sup> at baseline to  $44\pm12$  kdynes/cm<sup>2</sup> (p<0.001) 30 minutes after food intake, and  $58\pm13$  kdynes/cm<sup>2</sup> (p<0.05) 110 minutes after the meal. The change is mostly due to an increase in posterior wall thickness (PWTs) and decrease in left ventricular inner diameter in end-systole (LVIDs), though these do not remain separately significant 110 minutes postprandially. There was no significant change in systolic blood pressure, and thus the change is not driven by blood pressure but by myocardial contractility.



**Figure 7**. Circumferential end-systolic wall stress (cESS) at baseline before the meal, and 30 minutes and 110 minutes after the meal. cESS decreased significantly from 98±24 kdynes/cm<sup>2</sup> at baseline to 67±18 kdynes/cm<sup>2</sup> (p<0.001) 30 minutes after food intake, and 87±19 kdynes/cm<sup>2</sup> (p<0.01) 110 minutes after the meal. The percent change was 32% 30 minutes postprandially and 11% 110 minutes postprandially for both meridional wall stress (ESS) and circumferential wall stress (cESS).

# Paper II

The systolic tissue Doppler velocities at all sites except for the inferolateral wall increased significantly after the meal. The greatest increase was measured in the right ventricle 30 minutes postprandially, with a 24% difference compared to baseline. In the left ventricle at 30 minutes, the increase was 15% at the septal wall, 14% at the anteroseptal wall, and 12% at the lateral wall. The average increase for the total left ventricle was 11% at 30 minutes after food intake. After 110 minutes a significant increase of myocardial velocities remained at the right ventricle, anteroseptal and septal walls of the left ventricle, and for the composite of the left ventricle. The absolute numbers of some of the measurements (SV, CO, s' septal and lateral) in paper II differs very slightly from previously reported numbers [114] and those presented for the same population in paper III and IV, since not all subjects are included. Table 3 shows an overview of the findings.

Variable	Fasting	30 min after food intake	110 min after food intake
SV (ml)	67±13	80±16 ***	71±13 **
CO (L/min)	4.05±0.88	5.28±1.02 ***	4.23±0.78
Heart rate (bpm)	60±8	66±10 **	60±10
Systolic BP (mm Hg)	103±10	103±10	102±10
Diastolic BP (mm Hg)	67±7	59±8 ***	63±6 *
s´ (right ventricle) (cm/s)	13.1±1.9	16.2±3.0 ***	14.5±2.1 ***
s´ (septal) (cm/s)	8.4±0.8	9.7±1.2 ***	9.4±1.2 ***
s´ (lateral) (cm/s)	12.5±2.4	14.0±2.4 *	13.3±2.9
s´ (inferior) (cm/s)	10.2±1.7	11.2±1.2 *	10.9±1.7
s´ (anterior) (cm/s)	10.9±1.8	11.6±1.8 *	11.4±2.5
s´ (inferolateral) (cm/s)	11.9±1.9	12.9±2.8	12.6±2.2
s' (anteroseptal) (cm/s)	8.1±1.2	9.2±1.3 ***	8.7±1.0 *
s' (composite left ventricle) (cm/s)	10.3±1.2	11.4±1.4***	11.1±1.6 *

 Table 3. (n=19). Values are mean ± SD.

Abbreviations: Blood pressure (BP), left ventricular stroke volume (SV), and left ventricular cardiac output (CO). Pulsed tissue Doppler peak systolic velocities (s'). \*Indicates significant difference (p<0.05), compared to fasting values.

\*\*Indicates significant difference (p<0.01), compared to fasting values.

\*\*\*Indicates significant difference (p<0.001), compared to fasting values.

### Paper III

Myocardial performance index decreased significantly (p<0.001) 30 minutes after food intake, from  $0.28\pm0.06$  to  $0.20\pm0.07$ , which is a percent change of 29% (Figure 8). More specifically, the sum of isovolumetric contraction time (ICT) + ejection time (ET) + isovolumetric relaxation time (IRT) (a in Figure 1) decreased from  $0.400\pm0.024$  ms at baseline to  $0.370\pm0.016$  ms (p<0.001) 30 minutes after the meal, whereas the change in ET (b in Figure 1) was only from  $0.313\pm0.016$  ms to  $0.309\pm0.016$  ms (p<0.05). No significant change of MPI was seen at 110 minutes after the meal, though the sum of ICT+ET+IRT remained significantly decreased ( $0.391\pm0.023$  ms (p<0.05)) whereas the change in ET was nonsignificant.



**Figure 8.** Myocardial performance index (MPI) at baseline before the meal and 30 minutes and 110 minutes after the meal. MPI decreased significantly from  $0.28\pm0.06$  at baseline to  $0.20\pm0.07$  (p<0.001) 30 minutes after food intake, and  $0.26\pm0.06$  (non-significant) 110 minutes after the meal. The main alteration was the decrease in isovolumetric contraction time (ICT) + isovolumetric relaxation time (IRT).

# Paper IV

Of the 30 subjects, 29 are included at 180 minutes after food intake, due to a late arrival. Left ventricular wall stress could not be calculated in two subjects because of immeasurable M-mode tracings, and in one participant short axis was used because long axis could not be obtained. Because of a mild aortic insufficiency E/A, E/e', and MPI could not be calculated in one subject. In one case, SV, CO, and CI could not be calculated 30 minutes after the meal because storage of LVOT VTI failed. Descriptive characteristics and cardiac dimensions of the study population at baseline are shown in Table 4.

Variable	
Sex (male/female)	15/15
Body mass (kg)	72±14
Height (cm)	172±11
BMI (kg/m <sup>2</sup> )	24.2±2.9
BSA (m <sup>2</sup> )	1.8±0.2
LVIDd (mm/m <sup>2</sup> )	27.6±3.4
LVIDs (mm/m <sup>2</sup> )	15.4±2.5
IVSd (mm/m <sup>2</sup> )	5.4±0.6
PWTd (mm/m <sup>2</sup> )	5.1±0.6
LA (mm/m <sup>2</sup> )	22.3±3.0
LVM (g/m <sup>2</sup> )	95.5±19.8

Table 4. Descriptive statistics and cardiac dimensions. Values are mean ± SD.

Abbreviations: Indexed for body surface area (BSA): Left ventricular inner diameter in end-diastole (LVIDd), Left ventricular inner diameter in end-systole (LVIDs), Interventricular septum thickness (IVSd), Posterior wall thickness (PWTd), Left atrial end-systolic diameter (LA), and Left ventricular mass (LVM).

Several changes were seen 30 minutes after the meal. Table 5 tries to give a comprehensive overview of all measured and calculated parameters at specific times.

Variable	Fasting	30 minutes aftefood	90 minutes	180 minutes after
SV (ml)	80±21	91±24***	86±24**	81±22
CO (L/min)	5.05±1.28	5.88±1.42***	5.07±1.23	4.71±1.22*
CI (L/min/m <sup>2</sup> )	2.75±0.58	3.24±0.73***	2.77±0.57	2.58±0.58**
Heart rate (bpm)	63±9	66±9*	60±7*	59±7**
Systolic BP (mm Hg)	127±13	123±14*	124±15	130±16
Diastolic BP (mm Hg)	79±8	72±11***	74±9***	79±11
LVOT VTI (cm)	24.3±2.8	27.7±4.6***	25.8±3.6**	24.4±3.3
E (cm/s)	69.9±9.8	79.3±15.3***	71.0±15.4	69.2±12.4
A (cm/s)	73.2±12.2	77.7±14.9*	70.9±12.0	71.3±13.9
E/A	1.0±0.2	1.1±0.4*	1.0±0.3	1.0±0.3
S (cm/s)	56.0±8.4	61.4±10.9**	55.7±10.3	53.1±7.5
D (cm/s)	39.1±10.0	43.8±9.6**	38.4±8.8	36.4±8.4
S/D	1.5±0.3	1.4±0.3	1.5±0.3	1.5±0.3
DT (msec)	193.7±37.3	199.3±33.6	216.7±39.5**	209.0±33.7*
s´ (septal) (cm/s)	8.6±1.6	9.7±1.4***	8.8±1.2	8.3±1.4
e´ (septal) (cm/s)	8.1±1.7	8.8±1.7**	8.2±1.8	7.6±1.7*
a´ (septal) (cm/s)	9.7±1.8	10.9±1.9***	10.3±2.0*	9.8±1.7
s´ (lateral) (cm/s)	9.4±2.2	10.5±2.1***	9.7±1.9	9.1±1.7
e´ (lateral) (cm/s)	10.3±2.5	10.9±2.4	10.5±2.6	9.8±2.6
a´ (lateral) (cm/s)	9.9±1.8	10.5±2.0*	10.2±2.2	10.1±1.9
E/e´ (average)	7.8±1.7	8.1±2.0	7.7±2.1	8.2±2.2
E/e´ (septal)	8.9±2.2	9.1±2.0	8.7±2.2	9.3±2.3
E/e´ (lateral)	7.1±1.9	7.5±2.3	7.0±2.1	7.5±2.4
s' (right ventricle) (cm/s)	14.0±2.6	16.3±3.4***	14.7±2.4*	14.4±2.9
GLS (%)	22.7±2.2	24.5±2.3***	23.4±2.1*	22.9±2.1
ESS (kdynes/cm <sup>2</sup> )	56.7±21.6	31.2±10.3***	39.4±14.0***	51.0±15.6
cESS (kdynes/cm <sup>2</sup> )	84.9±32.4	46.7±15.4***	59.0±20.9***	76.4±23.7
MPI	0.36±0.1	0.24±0.1***	0.30±0.1***	0.35±0.1
MAPSE septal (mm)	12.9±2.1	14.9±2.6***	13.4±2.2	13.0±2.1
MAPSE lateral (mm)	14.1±2.4	16.8±3.1***	15.5±2.6**	14.5±2.6
MAPSE inferior (mm)	13.9±2.7	15.8±2.9***	14.1±2.7	13.3±2.5
MAPSE anterior (mm)	13.3±2.2	14.8±2.7**	13.7±2.6	12.9±2.2
TAPSE (mm)	24.1±4.3	27.3±4.6***	25.7±4.6**	24.8±3.9

**Table 5.** Hemodynamics, blood pressure, heart rate, pulsed Doppler, and tissue Doppler parameters before and 30, 90, and 180 minutes after a standardized meal. Values are mean ± standard deviation.

Abbreviations: Left ventricular stroke volume (SV); Left ventricular cardiac output (CO); Cardiac index (CI); Blood pressure (BP); Left ventricular outflow velocity-time integral (LVOT VTI); Peak of early diastolic (E) and late diastolic (A) mitral flow velocities; Pulmonary vein peak velocities in systole (S) and in diastole (D); Deceleration time of E-wave (DT); Pulsed tissue Doppler velocities: peak systolic (s'), early (e'), and late (a') diastolic velocities; Right ventricular free wall peak systolic pulsed tissue Doppler velocities (s' right ventricle); Global longitudinal strain (GLS); Meridional end-systolic wall stress (ESS); Circumferential end-systolic wall stress (cESS); Myocardial performance index (MPI); Mitral annular plane systolic excursion (MAPSE); and Tricuspid annular plane systolic excursion (TAPSE).

\*Indicates significant difference (p<0.05), compared to fasting values.

\*\*Indicates significant difference (p<0.01), compared to fasting values.

\*\*\*Indicates significant difference (p<0.001), compared to fasting values.

Hemodynamically, at 30 minutes there was an increase in CO (16%) with an increase in stroke volume (14%) and a reduction of blood pressure, especially diastolic (9%). Cardiac index increased by 19%. Of the other echocardiographic parameters, left ventricular wall stress and MPI showed the biggest changes. Both ESS and cESS were decreased by 45% at 30 minutes and still 31% below baseline at 90 minutes. MPI was lowered by 33% at 30 minutes and by 17% at 90 minutes.

Amongst the other pulsed wave Doppler and tissue Doppler parameters, the larger changes were seen in MAPSE (lateral) (19%), MAPSE (septal) (16%), and s' (right ventricle) (16%). Besides SV, there was a 14% increase in E, MAPSE (inferior), and LVOT VTI. A 13% increase was seen in TAPSE and s'(septal), and a 12% increase was seen in s'(lateral), a' (septal), and D. Significant changes at 30 minutes were also seen in MAPSE (anterior) (11%), S and E/A ratio (both 10%), e'(septal) (9%), GLS (8%), and a' (lateral) and A (both 6%). In addition to wall stress and MPI there were still some significant changes in Doppler parameters 90 minutes after food intake, although most of the variables had returned to baseline. There was an increase of 3-9% compared to fasting values in MAPSE (lateral), TAPSE, GLS, SV, LVOT VTI, a' (septal), and s' (right ventricle). There was also a significant increase in DT (12%). Diastolic blood pressure was still reduced by 6%. SV was still increased (8%) though there was a decrease in heart rate (5%) and therefore no significant remaining change in cardiac output. None of the significant changes seen at 30 minutes remained 180 minutes after the meal. Cardiac output, cardiac index, and heart rate were significantly lowered as was e' (septal) while DT remained increased.

# Discussion

Our studies show that food intake affects several echocardiographic variables in both a younger and an older population. Parameters used to assess both systolic and diastolic function were affected. The changes were mostly present 30 minutes after a meal but some of the measured parameters remained significant 90 and 110 minutes postprandially. We have examined two different age groups and found differences but also many similarities, both in the changes seen after food intake and in baseline measurements.

It is common knowledge that digestion of food affects hemodynamics. Although the exact mechanisms behind the findings are still unclear, we know there is a postprandial alteration of loading conditions as cardiac output increases and diastolic blood pressure decreases while the blood flow increases to the gastrointestinal tract [57, 59, 60, 62]. A previous study on our young population has suggested that physiological changes in some hormones connected to food intake (insulin, grehlin, and GLP-1) as well as glucose may influence the activity of the heart [108]. Insulin is known to have positive inotropic and chronotropic effects on the heart [67]. An improvement of left ventricular function has been attributed to GLP-1 [109, 110], while ghrelin has been shown to increase SV and CO [111]. Echocardiography is a widely used, easily accessible way of examining the heart in many various contexts, and the fact that some parameters change after a meal does not seem far-fetched. Still, food consumption is not mentioned as a factor in echocardiographic investigations.

The first examination after food intake was made 30 minutes afterwards in both study populations. In the young population (papers I-III and an earlier study [105]), the second follow-up was made 110 minutes postprandially, but because not all variables were back at baseline by then we choose to prolong the observation time but shorten the interval between examinations in the older population (paper IV), with follow-up exams at 30, 90, and 180 minutes postprandially. There are a large number of investigated variables that will be discussed and compared between the populations. Table 6 displays a percentage comparison 30 minutes after food intake as an effort to make it more comprehensible.

# **Baseline findings**

The anthropometric characteristics and cardiac dimensions of the two age groups were quite similar except for a bigger left atrium in the older population. At baseline, the young population had in general lower blood pressure and a slightly lower heart rate, lower CO and SV with a lower LVOT VTI. Regarding tissue Doppler, the only major difference in the systolic and diastolic parameters was that e'(lateral) was much higher in the young population. Less pronounced was a similar difference in e'(septal) and s'(lateral). As could be expected considering known diastolic changes related to age, the E/A ratio also was much higher in the young population, while the S/D ratio was lower. Left ventricular end-systolic wall stress, while not used in clinical practice, is a research variable that has been used in various investigations as an index of myocardial afterload [112-116]. Both ESS and cESS were higher in the young subjects. The lower index value at baseline in the older population is in line with the common changes related to age with increased wall thickness and fibrosis, although no definitive differences were seen in PWTd and IVSd. The thicker wall has less wall stress, even if the intraventricular pressure is the same. However, earlier studies regarding age-related changes of ESS and cESS for the left ventricle have not shown any age difference [117]. Myocardial performance index, a Doppler-derived index, which has been suggested to reflect both systolic and diastolic function, was introduced by Tei in 1995 [118] and has mainly been used in the context of research. It was lower in the young population, which is consistent with earlier studies [74, 119]. The difference was seen in the ICT+IRT and could be caused by an increase in IRT related to age.

# Changes 30 minutes after food intake

In both the younger and older populations, the biggest change compared to fasting values were seen in left ventricular end-systolic wall stress. ESS and cESS were equally affected. There was a slight decrease in SBP in the older subjects, but the changes were mainly driven by myocardial contractility, with an increase in PWTs and a decrease in LVIDs. Fluid loading has previously been found to increase wall stress, and the application of glyceryl trinitrate has been found to cause a decrease in wall stress in patients undergoing routine coronary angiography [120]. With the altered loading conditions seen postprandially it is not surprising that wall stress is affected.

Another variable that was considerably affected in both groups was myocardial performance index (MPI). It has been investigated in many various populations over the last decades, both in adults as well as pediatric groups [121-132]. The decrease

in MPI was caused by a shortening of ICT + IRT with almost no change in ET (Figure 1). MPI is known to be affected by changes in afterload [133]. Given the hemodynamic changes seen postprandially, with altered loading conditions and increased CO, it is not surprising that MPI, and more specifically the isovolumetric relaxation and contraction, also changes.

As expected from previously reported postprandial hemodynamic changes [57, 59, 67] there was an increase in SV, CO, and LVOT VTI following an increased blood flow in the mesenteric arteries, while the diastolic blood pressure was lowered. Other systolic variables that were significantly affected in the older population in paper IV (not analyzed in the earlier studied younger group) was MAPSE and TAPSE, the longitudinal shortening of the left and right ventricle that increased as did GLS. Global longitudinal strain is increasingly used to measure left ventricular function. For example, in a report monitoring potential cardiotoxicity effects of chemo in cancer patients [134], a relative reduction in GLS of more than 10-15% from baseline values was considered a significant change. In comparison, we saw an increase in GLS of 8% 30 minutes after food intake. This suggests that results are influenced by varying fasting/food intake conditions, and not taking this into account is risky especially when making serial echocardiographic evaluations.

There was an increase in both systolic and diastolic tissue Doppler parameters in our studies, where s' of the right ventricle showed a larger change than s' of the left ventricle in both populations. The percent change was larger in general in the young population and remained significant for a longer time. Among the diastolic parameters, a'(lateral) stood out especially, with a larger and more lasting increase [105], while e'(septal) was the exception with a significant change only in the older population.

Regarding other diastolic measurements, the pulmonary vein peak velocities also changed significantly in both populations, with S showing twice the relative increase compared to baseline in the young. While E and A showed significant change in both populations, E/A did so only in the older group where E had the much larger increase, while the opposite was seen in the young with a dominating increase in A. As mentioned earlier, E was lower and A higher at baseline in the older population, which corresponds to the left ventricle becoming stiffer with age, with a prolonged relaxation and more significant late diastolic filling. This might make room for more optimization of the early diastolic filling as SV increases postprandially, and we saw a significant increase of E and E/A in the older, but not in the younger population. While no significant change was seen in DT at 30 minutes in the older population, a previous study [105] has shown a significant decrease of 15% compared to baseline in the young population. DT was about the same at baseline in the two groups, although it is otherwise shown to usually be prolonged with age [135].

Variable	Percent change 30 minutes after food intake in younger adults (%)	Percent change 30 minutes after food intake in healthy elderly (%)
SV	19***	14***
со	30***	16***
Heart rate	10**	5*
Systolic BP	0	3*
Diastolic BP	12**	9***
LVOT VTI	20***	14***
E	8**	14***
A	15**	6*
E/A	5	10*
S	20***	10**
D	12***	12**
S/D	7*	7
DT	15***	3
s´ (septal)	15***	13***
e´ (septal)	3	9**
a´ (septal)	14***	12***
s´ (lateral)	12**	12***
e´ (lateral)	7	6
a´ (lateral)	26***	6*
E/e´ (average)	2	4
E/e´ (septal)	5	2
E/e´ (lateral)	0	6
s´ (right ventricle)	24***	16***
MPI	29***	33***
ESS	32***	45***
cESS	32***	45***

**Table 6.** Comparison for percent change 30 minutes after food intake for select variables between studies of the younger adults and the healthy elderly.

**Abbreviations:** Left ventricular stroke volume (SV); Left ventricular cardiac output (CO); Blood pressure (BP); Left ventricular outflow velocity-time integral (LVOT VTI); Peak of early diastolic (E) and late diastolic (A) mitral flow velocities; Pulmonary vein peak velocities in systole (S) and in diastole (D); Deceleration time of E-wave (DT); Pulsed tissue Doppler velocities: peak systolic (s'), early (e'), and late (a') diastolic velocities; Right ventricular free wall peak systolic pulsed tissue Doppler velocities (s' right ventricle); Myocardial performance index (MPI); Meridional end-systolic wall stress (ESS); and Circumferential end-systolic wall stress (cESS).

\*Indicates significant difference (p<0.05), compared to fasting values for each study.

\*\*Indicates significant difference (p<0.01), compared to fasting values for each study.

\*\*\*Indicates significant difference (p<0.001), compared to fasting values for each study.

## Changes 90, 110, and 180 minutes after food intake

In the older population, a substantial decrease in both wall stress (cESS and ESS) and MPI remained at 90 minutes. Of the systolic measurements, GLS, MAPSE, TAPSE, s' (right ventricle), LVOT VTI and SV remained significantly increased while only a'(septal) remained significantly altered of the diastolic variables. The increase in DT was now significant and remained so after 180 minutes. This could agree with the usual prolongation of DT seen with increasing age [135] with a different response in the older group compared to the fast decrease seen in the young group, even if fasting values did not differ in our studies.

At 180 minutes there was also a significant decrease in HR, CO, CI, and e'(septal), which might be because of the long supine rest. All measurements were back around baseline (or on the opposite side from initial changes) at 180 minutes.

At 110 minutes a significant decrease in both wall stress and MPI still remained altered in the young population, as did an increase in SV, LVOT VTI, and the tissue Doppler measurements s' (right ventricle), s'(septal), s'(anteroseptal), and s' (composite left ventricle) of the systolic parameters. Of the diastolic measurements, only a'(lateral) and DT remained significantly altered.

By and large when comparing the two age groups, the young population showed greater changes in SV, LVOT VTI, CO, and pulsed tissue Doppler parameters (a difference of 2-20%) while larger decreases in wall stress (13%) and MPI (4%) were found in the older group. The longer isovolumetric (relaxation) time in the older group seen already at baseline might give room for a larger optimization than amongst the young, following the same line of reasoning as for the larger increase seen in E and E/A.

### Food intake and echocardiography

Postprandial changes in CO and SV have been described in several studies [57, 60, 61, 108]. To our knowledge, two previous studies have investigated the effect of food intake on pulsed wave Doppler, and in one case, also tissue Doppler parameters. Both studies investigated patients with hypertrophic cardiomyopathy together with 10 healthy controls fasting 30 minutes after food intake [136, 137]. The findings were, for most part, concordant with ours. In the first study [147], there was a significant change in E and not A, or E/A postprandially. In a more recent study [136], the healthy controls had significantly increased E and A, as did our populations, but no difference in E/A, which also is in concordance with our younger group. They also were investigated with tissue Doppler, and the mitral annular tissue velocity (e') was found to be higher and E/e' was found to be lower,

while we found no significant change in E/e'. Age difference and the small number of healthy participants are factors that could contribute to these differences. The meal size also was considerably larger in the second study (740 kcal compared to our 330 kcal) with a higher fat content and the inclusion of oral fluids. Oral intake of exogenous ketones also has been shown to affect cardiac function in healthy participants investigated with echocardiography [148].

A new study, published in October 2023, has investigated the influence of food intake and preload augmentation on cardiac functional parameters [40] using both CMR and TTE. The 82 participants were assessed before and after a fast infusion of 2 L isotonic saline, and half of them also had a meal consisting of a sandwich, a soda, and coffee/tea during the infusion. EDV and ESV and feature tracking (FT) were analyzed using CMR while GLS, and right ventricle longitudinal strain were analyzed from TTE. Both left ventricle and right ventricle were investigated. The study found that CO and left ventricle contractility were significantly increased by preload augmentation and further increased by food intake. The authors also state the risk of false improvement of GLS results after fluid infusion and food intake, which may affect follow-up examinations. With the knowledge gained in this thesis, it is interesting to read another study investigating the effects of food intake on cardiac parameters, also using another modality and adding preload augmentation with intravenous fluid. The findings are in many ways in line with ours, although the circumstances and modalities differ somewhat. In addition to the use of CMR and preload augmentation, the study groups differ regarding age and heart disease: half of the subjects had a known heart disease. The composition of the meal was different, and the food/fluid group also had an intake of oral fluids and caffeine. There is a time difference regarding the second TTE, since CMR was performed right after the infusion/meal. Global longitudinal strain was found to increase after only fluid infusion and after food/fluid with no significant difference between the groups. Feature tracking, on the other hand, was more improved in the food/fluid group. Here the longer time to follow-up with TTE could perhaps matter. The GLS at baseline is higher in our study population, although they are older, and our vendor is known to have slightly lower values [54]. This could perhaps be related to the participants with heart disease. Both our populations had lower SV and CO, but higher HR. The SV is calculated by different modalities, where CMR is "gold standard" and echocardiography is known to underestimate SV [138]. The occurrence of severe aortic valve regurgitations when subjects with cardiac disease were included might also contribute to the difference. Another interesting finding in the food intake/preload study was seemingly different ways for the left ventricle and right ventricle, respectively, to increase CO and SV: the left ventricle by increased contractility and the right ventricle by volume expansion.

So, we know that food intake affects hemodynamics, and we have an easily accessible and often-used diagnostic modality that can provide detailed data. Although echocardiography is such a commonly used investigation modality, we have not, with a few exceptions where food intake was the actual purpose [40, 136, 137], found the lapse of time between last food intake and examination to be mentioned in any echocardiographical studies or standardized. The subject of food intake also is not raised in guidelines or position papers [55, 83, 87]. In our studies, we found that food intake affects several echocardiographic variables in populations of different ages. Also, a previous investigation in our young population reported that food intake affected commonly used pulsed Doppler and tissue Doppler measurements [105]. All in all, our findings are not very surprising. While it is neither possible nor meaningful to adjust echocardiographic examinations in clinical practise after patients' food consumption, it is a factor that should be considered especially, in studies where the investigated population is small and in serial investigations of individuals.

### Limitations

The studies have, of course, limitations. One is our inability to make the single observer performing the exams blinded to the state of food intake. All exams were stored digitally, and for the first three papers, the measurements were performed later in random order to minimize bias. In the last study, however, this was not a feasible approach due to the amount of data and the limited time.

We did not include a control group that remained fasting. With more time and resources, a larger study material would have been desirable as would investigating men and women separately.

All measurements could not be made simultaneously during the exams, and the exact time frame, therefore, varies slightly for different parameters. Regarding the comparison between the investigations of the young and older population, the 10-year time lapse must be taken into account, with echocardiographic equipment from different technological generations being used. As an example, GLS was not possible to assess on the older machine. There also is a known difference between vendors, and our findings may not be true for another system than Phillips.

We used different methods to measure blood pressure in the two groups. Another limitation in the studies lies in the absence of measurements concerning changes in postprandial blood flow in the superior mesenteric artery following food intake. Postprandial refers to the period after eating a meal, and the superior mesenteric artery is a major blood vessel that supplies blood to the intestines, playing a crucial role in nutrient absorption and digestion. The lack of measurements in this context hampers a comprehensive understanding of how the circulatory system responds to the ingestion of food. Postprandial blood flow in the superior mesenteric artery is expected to undergo significant alterations to accommodate the increased demand for blood supply to the intestines during digestion and absorption. The inability to quantify these changes means that we may miss valuable insights into the dynamic vascular responses associated with the digestive process. To address this limitation, future research could consider incorporating techniques or methodologies that allow for the measurement of postprandial blood flow in the superior mesenteric artery, providing a more comprehensive understanding of the vascular dynamics during and after the consumption of a meal.

There was also a slight difference in protein and fat content in the digested porridge. The meal of breakfast porridge ingested in our studies was high in carbohydrates, and the results might differ after a meal of predominantly fat or protein, and with a meal of different size. Intake of caffeine, alcohol, or just oral fluids with the meal might also give another cardiovascular response. Smoking also has been shown to affect the diastolic function [139]. We don't know how alteration of loading conditions with, for example, intravenous fluids would have affected the response to food intake. Our study subjects were all without known cardiac disease, and the results are likely to differ in various patient groups, and with the use of various cardiovascular medications.

It is well known that prolonged, intensive exercise training leads to cardiac remodelling. We did not evaluate the level of daily physical activity or exercise capacity, and it is reasonable to believe both the younger and the older population were rather sedentary in their lifestyle. In addition, none of the data for wall stress, MPI, TDI, GLS, MAPSE, TAPSE or hemodynamic measurements were adjusted for heart rate because this is not done in clinical practice or in different investigations when using these measurements. All examinations were performed at rest and we, therefore, have no information about what happens with measured variables during exercise.

# Conclusions

Our studies show that several echocardiographic parameters reflecting both systolic and diastolic function are affected by food intake. More specifically:

- I. Left ventricular wall stress is affected by food intake in healthy young subjects. Both ESS and cESS were significantly reduced and showed a decrease of 32% compared to baseline 30 minutes after the meal. They were still significantly diminished 110 minutes afterwards. The change was driven by an increase in PWTs and a decrease in LVIDs.
- II. Left and right ventricular systolic tissue Doppler measurements are affected by food intake in healthy young subjects. Except for the inferolateral wall s' at all sites increased significantly after the meal. The largest change was measured in the right ventricle 30 minutes postprandially, with a difference of 24% compared to baseline. Both s' (right ventricle) and some sites in the left ventricle were still significantly increased after 110 minutes.
- III. Myocardial performance index is affected by food intake in healthy young subjects. It decreased significantly 30 minutes after food intake, from 0.28±0.06 to 0.20±0.07, which is a percent change of -29%. The decrease in MPI was caused by a shortening of ICT + IRT, with almost no change in ET.
- IV. Food intake affects systolic and diastolic echocardiographic measurements in healthy seniors. With a few exceptions, the findings are generally slightly less pronounced in the older population compared to younger subjects, which is to be expected considering changes in the cardiovascular system that comes about with advancing age.

Though it's difficult to implement our findings in daily clinical practice they suggest that the influence of food intake should be considered in studies, especially when the sample size is small, and most importantly, in serial investigations of individuals.

# Future perspectives

Although the findings are not relevant to echocardiographic examinations in everyday clinical practice, they suggest that food intake should be taken into consideration in studies, especially when the investigated population is small. It would be desirable to investigate a much larger population to see whether the approximate magnitude of the results can be confirmed, as well as to analyze men and women separately, since the results might differ. There are many other population groups and scenarios that would be interesting to investigate, since food intake is basic, and echocardiography is widely used and easily accessible. It could, for example, be interesting to evaluate populations with various cardiovascular diseases and medications, such as hypertension treated with beta-blockers, or patients with heart failure or cardiomyopathy. Also to study individuals with different body size (i.e very slim or obese), as all individuals studied in this thesis hade an average body composition. Another interesting aspect is diet. Further studies could investigate whether the findings also are valid for diets with high content of fat or protein, as well as for various meal sizes. The influence of caffeine, alcohol, and/or other oral fluids that often accompanies a meal is another aspect that would be interesting to study. As would the effect of smoking, which for some people also is a natural part of the meal procedure and has been shown to influence diastolic function. Studies examining how various loading conditions such as preload augmentation with intravenous fluids might influence the response to food intake could also be a future field of investigation. Further, it would be interesting to study if the cardiac response to exercise is affected after food intake, and if there are differences depending on levels of habitual physical activity.

There are other imaging modalities where measurements also might be affected by hemodynamic changes after food intake, for example, CMR (as some parameters were shown to be in a recent study [40]. In future studies, addressing the limitation of not measuring postprandial blood flow in the superior mesenteric artery could also involve CMR. Designing well-controlled studies, recruiting diverse participants, and integrating CMR data with complementary measurements will contribute to a more comprehensive understanding of postprandial vascular dynamics in the superior mesenteric artery.

More studies in this neighbouring field could be of value. As addressed in the introduction, the emerging Sodium glucose cotransporter-2 inhibitors and GLP-1

agonists would be interesting to evaluate in the context of food intake and echocardiography measurements. All of these to explore different aspects of the gastro-cardiac connection.

# Errata

# Paper I

Ref 14: WH Gaasch, inte WS.

Ref 20. Published in J. Clin End 2001 not 2010.

Ref 22: do not exist, was confused with ref 21 and 17.

# Paper II

Missing reference: Gilligan D, Marsonis A, Joshi Jayshree, Nihoyannopoulos P, Ghatei, M, Bloom S, Oakley C. Cardiovascular and Hormonal Responses to a Meal in Hypertrophic Cardiomyopathy: A Comparison of patients with and without Postprandial Exacerbation of Symptoms. Clin Cardiol (1996); 19: 129-135.

References that were part of the reference list but not incorporated in the text:

Waaler BA, Eriksen M, Toska K. The effect of meal size on postprandial increase in cardiac output. Acta Physiol Scand (1991); 142: 33-9.

Waaler BA, Hisdal J, Eriksen M. Circulatory responses to a meal in patients with a newly transplanted heart. Acta Physiol Scand (2002); 174: 101-8.

### Paper III

Abstract and Figure 2: The significance of the change in MPI 30 minutes after food intake has p < 0.001 (says p < 0.05).

Ref 2 should be: Ärnlöv J, Ingelsson E, Risérus U, Andrén B, Lind L: Myocardial performance index, a Doppler-derived index of global left ventricular function, predicts congestive heart failure in elderly men. *European Heart Journal* 2004, 25: 2220-2225

### Paper IV

Results: Though most variables had returned to baseline, there were still significant changes in some Doppler parameters 90 minutes after food intake, with an increase in MAPSE (lateral), TAPSE, GLS, SV, LVOT, VTI, a'(septal) and s'(right ventricle) by 3-9% (not 3-12%) compared to fasting values.

# Acknowledgements

There are many people who in various big and smaller ways have made this thesis possible. I especially want to mention some.

First, I would like to thank my main supervisor, **Magnus Dencker** for getting me started on this surprisingly long journey. For guidance along the way, fast answers, pragmatic advice, and for listening when it counts. And sometimes not listening quite so much—which can be surprisingly helpful too.

My co-supervisor, **Joanna Hlebowicz Frisén**, who also got me started on this project a long time ago. Thank you for the conversations, input, and advice related to both science, work, and life. And extra help with statistics and knowledge of food-related hormones.

Another extremely valuable person is **Andreas Malmgren**. Thank you for your echocardiographic skill, your extensive knowledge your good advice as co-author, professional Biomedical Scientist, and fellow PhD student.

Anna Dieden, co-author and partner in ouzo gustation.

I would also like to thank my boss at the Department of Imaging and Functional studies, **Peter Hochbergs** for giving me the time and opportunity to explore this scientific work, and also Professors **Sophia Zackrisson** and **Pia Maly Sundgren**. Without "BoF-veckor," this thesis would not exist.

My fantastic colleagues and friends at the Unit of Radiology, especially the thoracic section—Anders, Idar, Lars, Kristin, Maria, Hanna, Adrian, Gracijela, Catharina, Pär, Lotta—and of the cardiac branch Isabel and Ellen. For all clinical work making this thesis possible, and for making me want to go work every (well most) days!

Elin, Sophia and Sabine, wise, wonderful colleagues in the Unit of Clinical Physiology and Nuclear Medicine with whom I can talk about both highs and lows in science, work, and life.

All the study participants who offered their time and willingly ate plain porridge for breakfast.

And, of course, my family. My parents, **Lolo** and **Ulf** who have always given me love and support—and lately been the best grandparents/babysitters. **Christoffer**, my partner who gives me perspective and widens my horizon. **Arvid** and **Linnea**, my darlings. And **Milla**, my furry friend and best companion in the woods.

# References

- 1. Smout AJMP, A.L., Normal and disturbed motility of the gastrointestinal tract. 1992: Wrightson Biomedical Publishing LTD, Petersfield.
- Aquilonius SM, F.J., Neurologi, tredje upplagan. 2000, Liber AB, Stockholm. p. p 40.
- 3. Guyton AC, H.J., Textbook of medical physiology, ninth edition. 1996: WB Saunders company, Philadelphia.
- 4. Van Neuten JM, S.J., Akkermans LMA, Gastro-pyloroduodenal cordination. 1990: Wrightson Biomedical Publishing, Petersfield.
- 5. Hunt, J.N., J.L. Smith, and C.L. Jiang, Effect of meal volume and energy density on the gastric emptying of carbohydrates. Gastroenterology, 1985. 89(6): p. 1326-30.
- 6. Russo, A., et al., Insulin-induced hypoglycemia accelerates gastric emptying of solids and liquids in long-standing type 1 diabetes. J Clin Endocrinol Metab, 2005. 90(8): p. 4489-95.
- 7. Schvarcz, E., et al., Hypoglycemia increases the gastric emptying rate in healthy subjects. Diabetes Care, 1995. 18(5): p. 674-6.
- 8. Schvarcz, E., et al., Hypoglycaemia increases the gastric emptying rate in patients with type 1 diabetes mellitus. Diabet Med, 1993. 10(7): p. 660-3.
- 9. Fraser, R.J., et al., Hyperglycaemia slows gastric emptying in type 1 (insulindependent) diabetes mellitus. Diabetologia, 1990. 33(11): p. 675-80.
- 10. MacGregor, I.L., et al., The effect of acute hyperglycemia on gastric emptying in man. Gastroenterology, 1976. 70(2): p. 190-6.
- Oster-Jørgensen, E., S.A. Pedersen, and M.L. Larsen, The influence of induced hyperglycaemia on gastric emptying rate in healthy humans. Scand J Clin Lab Invest, 1990. 50(8): p. 831-6.
- 12. Schvarcz, E., et al., Physiological hyperglycemia slows gastric emptying in normal subjects and patients with insulin-dependent diabetes mellitus. Gastroenterology, 1997. 113(1): p. 60-6.
- 13. Björnsson, E.S., et al., Effects of insulin and beta-adrenergic blockade on the migrating motor complex in humans. Scand J Gastroenterol, 1995. 30(3): p. 219-24.
- 14. Eliasson, B., et al., Hyperinsulinaemia impairs gastrointestinal motility and slows carbohydrate absorption. Diabetologia, 1995. 38(1): p. 79-85.
- 15. Lavigne, M.E., et al., Gastric emptying rates of solid food in relation to body size. Gastroenterology, 1978. 74(6): p. 1258-60.

- 16. Wisén, O. and P.M. Hellström, Gastrointestinal motility in obesity. J Intern Med, 1995. 237(4): p. 411-8.
- Hanson, M. and B. Lilja, Gastric emptying in smokers. Scand J Gastroenterol, 1987. 22(9): p. 1102-4.
- Sanaka, M., et al., Effect of cigarette smoking on gastric emptying of solids in Japanese smokers: a crossover study using the 13C-octanoic acid breath test. J Gastroenterol, 2005. 40(6): p. 578-82.
- 19. Datz, F.L., P.E. Christian, and J. Moore, Gender-related differences in gastric emptying. J Nucl Med, 1987. 28(7): p. 1204-7.
- 20. Hermansson, G. and R. Sivertsson, Gender-related differences in gastric emptying rate of solid meals. Dig Dis Sci, 1996. 41(10): p. 1994-8.
- 21. Hutson, W.R., R.L. Roehrkasse, and A. Wald, Influence of gender and menopause on gastric emptying and motility. Gastroenterology, 1989. 96(1): p. 11-7.
- 22. Varga, G., et al., Involvement of endogenous CCK and CCK1 receptors in colonic motor function. Br J Pharmacol, 2004. 141(8): p. 1275-84.
- 23. Nilsson, B.I., et al., Relationship between interdigestive gallbladder emptying, plasma motilin and migrating motor complex in man. Acta Physiol Scand, 1990. 139(1): p. 55-61.
- 24. Kruger, D.F., C.L. Martin, and C.E. Sadler, New insights into glucose regulation. Diabetes Educ, 2006. 32(2): p. 221-8.
- 25. Edvardsen, T., et al., Non-invasive imaging in coronary syndromes: recommendations of the European Association of Cardiovascular Imaging and the American Society of Echocardiography, in collaboration with the American Society of Nuclear Cardiology, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. Eur Heart J Cardiovasc Imaging, 2022. 23(2): p. e6-e33.
- 26. Näslund, E., et al., Energy intake and appetite are suppressed by glucagon-like peptide-1 (GLP-1) in obese men. Int J Obes Relat Metab Disord, 1999. 23(3): p. 304-11.
- 27. Näslund, E., et al., GLP-1 slows solid gastric emptying and inhibits insulin, glucagon, and PYY release in humans. Am J Physiol, 1999. 277(3): p. R910-6.
- 28. Näslund, E., et al., Glucagon-like peptide 1 increases the period of postprandial satiety and slows gastric emptying in obese men. Am J Clin Nutr, 1998. 68(3): p. 525-30.
- Nauck, M.A., et al., Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. Am J Physiol, 1997. 273(5): p. E981-8.
- 30. Wettergren, A., et al., Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. Dig Dis Sci, 1993. 38(4): p. 665-73.
- 31. Hall JE, G.A., Guyton and Hall textbook of medical physiology. 9th ed. 1996: Saunders Company.
- 32. Jonson B, W.H., White T, Wollmer P, Klinisk Fysiologi. 1st ed. 1998.

- 33. Mitchell, J.R. and J.J. Wang, Expanding application of the Wiggers diagram to teach cardiovascular physiology. Adv Physiol Educ, 2014. 38(2): p. 170-5.
- 34. Norton, J.M., Toward consistent definitions for preload and afterload. Adv Physiol Educ, 2001. 25(1-4): p. 53-61.
- 35. Sengupta, P.P., et al., Left ventricular structure and function: basic science for cardiac imaging. J Am Coll Cardiol, 2006. 48(10): p. 1988-2001.
- 36. Lang R, G.S., Kronzon I, Khandheria BK, Mor-Avi V, ASE's Comprehensive Echocardiography 2nd ed. 2016: Saunders/Elsevier.
- Buckberg, G. and J.I. Hoffman, Right ventricular architecture responsible for mechanical performance: unifying role of ventricular septum. J Thorac Cardiovasc Surg, 2014. 148(6): p. 3166-71.e1-4.
- 38. Kovács, A., et al., Right ventricular mechanical pattern in health and disease: beyond longitudinal shortening. Heart Fail Rev, 2019. 24(4): p. 511-520.
- 39. Sanz, J., et al., Anatomy, Function, and Dysfunction of the Right Ventricle: JACC State-of-the-Art Review. J Am Coll Cardiol, 2019. 73(12): p. 1463-1482.
- 40. Visby, L., et al., The Influence of Food Intake and Preload Augmentation on Cardiac Functional Parameters: A Study Using Both Cardiac Magnetic Resonance and Echocardiography. J Clin Med, 2023. 12(21).
- 41. Carlsson, M., et al., The quantitative relationship between longitudinal and radial function in left, right, and total heart pumping in humans. Am J Physiol Heart Circ Physiol, 2007. 293(1): p. H636-44.
- 42. Fleg, J.L. and J. Strait, Age-associated changes in cardiovascular structure and function: a fertile milieu for future disease. Heart Fail Rev, 2012. 17(4-5): p. 545-54.
- 43. Pugh, K.G. and J.Y. Wei, Clinical implications of physiological changes in the aging heart. Drugs Aging, 2001. 18(4): p. 263-76.
- 44. Salmasi, A.M., et al., Age-associated changes in left ventricular diastolic function are related to increasing left ventricular mass. Am J Hypertens, 2003. 16(6): p. 473-7.
- 45. Strait, J.B. and E.G. Lakatta, Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin, 2012. 8(1): p. 143-64.
- 46. Agrawal T, N.S., Changes in cardiac structure and function with aging. J Cardiovasc Aging, 2022.
- Kou, S., et al., Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study. Eur Heart J Cardiovasc Imaging, 2014. 15(6): p. 680-90.
- Støylen, A., H.E. Mølmen, and H. Dalen, Importance of length and external diameter in left ventricular geometry. Normal values from the HUNT Study. Open Heart, 2016. 3(2): p. e000465.
- 49. Olivetti, G., et al., Cardiomyopathy of the aging human heart. Myocyte loss and reactive cellular hypertrophy. Circ Res, 1991. 68(6): p. 1560-8.
- 50. Fiechter, M., et al., Age-related normal structural and functional ventricular values in cardiac function assessed by magnetic resonance. BMC Med Imaging, 2013. 13: p. 6.

- 51. Maffessanti, F., et al., Age-, body size-, and sex-specific reference values for right ventricular volumes and ejection fraction by three-dimensional echocardiography: a multicenter echocardiographic study in 507 healthy volunteers. Circ Cardiovasc Imaging, 2013. 6(5): p. 700-10.
- 52. Singh, A., et al., Normal Values of Left Atrial Size and Function and the Impact of Age: Results of the World Alliance Societies of Echocardiography Study. J Am Soc Echocardiogr, 2022. 35(2): p. 154-164.e3.
- 53. Soulat-Dufour, L., et al., Normal Values of Right Atrial Size and Function According to Age, Sex, and Ethnicity: Results of the World Alliance Societies of Echocardiography Study. J Am Soc Echocardiogr, 2021. 34(3): p. 286-300.
- 54. D'Elia, N., et al., Normal Global Longitudinal Strain: An Individual Patient Meta-Analysis. JACC Cardiovasc Imaging, 2020. 13(1 Pt 1): p. 167-169.
- 55. Nagueh, S.F., et al., Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr, 2016. 29(4): p. 277-314.
- Caballero, L., et al., Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. Eur Heart J Cardiovasc Imaging, 2015. 16(9): p. 1031-41.
- 57. Fagan, T.C., et al., Postprandial alterations in hemodynamics and blood pressure in normal subjects. Am J Cardiol, 1986. 58(7): p. 636-41.
- 58. Waaler, B.A. and M. Eriksen, Post-prandial cardiovascular responses in man after ingestion of carbohydrate, protein or fat. Acta Physiol Scand, 1992. 146(3): p. 321-7.
- 59. Waaler, B.A., M. Eriksen, and T. Janbu, The effect of a meal on cardiac output in man at rest and during moderate exercise. Acta Physiol Scand, 1990. 140(2): p. 167-73.
- 60. Ishimine, M., et al., Postprandial hemodynamic changes evaluated by a Doppler echocardiographic method. Jpn Heart J, 1994. 35(1): p. 35-42.
- 61. Kelbaek, H., et al., Central haemodynamic changes after a meal. Br Heart J, 1989. 61(6): p. 506-9.
- 62. Waaler, B.A., M. Eriksen, and K. Toska, The effect of meal size on postprandial increase in cardiac output. Acta Physiol Scand, 1991. 142(1): p. 33-9.
- 63. Gordan, R., J.K. Gwathmey, and L.H. Xie, Autonomic and endocrine control of cardiovascular function. World J Cardiol, 2015. 7(4): p. 204-14.
- 64. Waaler, B.A., J. Hisdal, and M. Eriksen, Circulatory responses to a meal in patients with a newly transplanted heart. Acta Physiol Scand, 2002. 174(2): p. 101-8.
- 65. Waaler, B.A., et al., Mechanisms behind the postprandial increase in cardiac output: a clue obtained from transplanted hearts. Eur J Appl Physiol, 2006. 97(5): p. 516-20.
- 66. Muniyappa, R., et al., Cardiovascular actions of insulin. Endocr Rev, 2007. 28(5): p. 463-91.
- 67. Baron, A.D., Hemodynamic actions of insulin. Am J Physiol, 1994. 267(2 Pt 1): p. E187-202.

- 68. Poher, A.L., M.H. Tschöp, and T.D. Müller, Ghrelin regulation of glucose metabolism. Peptides, 2018. 100: p. 236-242.
- 69. Galderisi, M., et al., Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging, 2017. 18(12): p. 1301-1310.
- 70. Rudski, L.G., et al., Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr, 2010. 23(7): p. 685-713; quiz 786-8.
- 71. Edler, I. and K. Lindström, The history of echocardiography. Ultrasound Med Biol, 2004. 30(12): p. 1565-644.
- 72. Johri, A.M., et al., ASE Statement on Point-of-Care Ultrasound during the 2019 Novel Coronavirus Pandemic. J Am Soc Echocardiogr, 2020. 33(6): p. 670-673.
- 73. Levitov, A., et al., Guidelines for the Appropriate Use of Bedside General and Cardiac Ultrasonography in the Evaluation of Critically Ill Patients-Part II: Cardiac Ultrasonography. Crit Care Med, 2016. 44(6): p. 1206-27.
- 74. Spencer, K.T., et al., Focused cardiac ultrasound: recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr, 2013. 26(6): p. 567-81.
- 75. Evangelista, A., et al., European Association of Echocardiography recommendations for standardization of performance, digital storage and reporting of echocardiographic studies. Eur J Echocardiogr, 2008. 9(4): p. 438-48.
- 76. Mitchell, C., et al., Guidelines for Performing a Comprehensive Transthoracic Echocardiographic Examination in Adults: Recommendations from the American Society of Echocardiography. J Am Soc Echocardiogr, 2019. 32(1): p. 1-64.
- 77. Potter, E. and T.H. Marwick, Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. JACC Cardiovasc Imaging, 2018. 11(2 Pt 1): p. 260-274.
- 78. Hung, J., et al., 3D echocardiography: a review of the current status and future directions. J Am Soc Echocardiogr, 2007. 20(3): p. 213-33.
- Porter, T.R., et al., Clinical Applications of Ultrasonic Enhancing Agents in Echocardiography: 2018 American Society of Echocardiography Guidelines Update. J Am Soc Echocardiogr, 2018. 31(3): p. 241-274.
- Senior, R., et al., Clinical practice of contrast echocardiography: recommendation by the European Association of Cardiovascular Imaging (EACVI) 2017. Eur Heart J Cardiovasc Imaging, 2017. 18(11): p. 1205-1205af.
- 81. Hoffmann, R., et al., Analysis of left ventricular volumes and function: a multicenter comparison of cardiac magnetic resonance imaging, cine ventriculography, and unenhanced and contrast-enhanced two-dimensional and three-dimensional echocardiography. J Am Soc Echocardiogr, 2014. 27(3): p. 292-301.

- Larsson, M.K., et al., The potential clinical value of contrast-enhanced echocardiography beyond current recommendations. Cardiovasc Ultrasound, 2016. 14: p. 2.
- Galderisi, M., et al., Recommendations of the European Association of Echocardiography: how to use echo-Doppler in clinical trials: different modalities for different purposes. Eur J Echocardiogr, 2011. 12(5): p. 339-53.
- 84. Dons, M., et al., Myocardial performance index by tissue Doppler echocardiography predicts adverse events in patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging, 2020. 21(5): p. 560-566.
- 85. Nakou, E.S., et al., Short-term effects of angiotensin receptor-neprilysin inhibitors on diastolic strain and tissue doppler parameters in heart failure patients with reduced ejection fraction: A pilot trial. Hellenic J Cardiol, 2020. 61(6): p. 415-418.
- 86. Tanaka, H., et al., Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure. Cardiovasc Diabetol, 2020. 19(1): p. 6.
- 87. Mor-Avi, V., et al., Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography. Eur J Echocardiogr, 2011. 12(3): p. 167-205.
- von Knobelsdorff-Brenkenhoff, F. and J. Schulz-Menger, Role of cardiovascular magnetic resonance in the guidelines of the European Society of Cardiology. J Cardiovasc Magn Reson, 2016. 18: p. 6.
- 89. Kramer, C.M., et al., Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson, 2020. 22(1): p. 17.
- Zhang, J., et al., High frame rate cardiac cine MRI for the evaluation of diastolic function and its direct correlation with echocardiography. J Magn Reson Imaging, 2019. 50(5): p. 1571-1582.
- 91. Abbara, S., et al., SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr, 2016. 10(6): p. 435-449.
- 92. Pontone, G., et al., Clinical applications of cardiac computed tomography: a consensus paper of the European Association of Cardiovascular Imaging-part II. Eur Heart J Cardiovasc Imaging, 2022. 23(4): p. e136-e161.
- 93. Pontone, G., et al., Clinical applications of cardiac computed tomography: a consensus paper of the European Association of Cardiovascular Imaging-part I. Eur Heart J Cardiovasc Imaging, 2022. 23(3): p. 299-314.
- 94. Kaniewska, M., et al., Noninvasive evaluation of global and regional left ventricular function using computed tomography and magnetic resonance imaging: a metaanalysis. Eur Radiol, 2017. 27(4): p. 1640-1659.
- 95. Zdanowicz, A., et al., Dynamic CT Myocardial Perfusion: The Role of Functional Evaluation in the Diagnosis of Coronary Artery Disease. J Clin Med, 2023. 12(22).

- Dilsizian, V., et al., ASNC imaging guidelines/SNMMI procedure standard for positron emission tomography (PET) nuclear cardiology procedures. J Nucl Cardiol, 2016. 23(5): p. 1187-1226.
- 97. Henzlova, M.J., et al., ASNC imaging guidelines for SPECT nuclear cardiology procedures: Stress, protocols, and tracers. J Nucl Cardiol, 2016. 23(3): p. 606-39.
- Hesse, B., et al., EANM/ESC guidelines for radionuclide imaging of cardiac function. Eur J Nucl Med Mol Imaging, 2008. 35(4): p. 851-85.
- 99. Sciagrà, R., et al., EANM procedural guidelines for PET/CT quantitative myocardial perfusion imaging. Eur J Nucl Med Mol Imaging, 2021. 48(4): p. 1040-1069.
- 100. Verberne, H.J., et al., EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. Eur J Nucl Med Mol Imaging, 2015. 42(12): p. 1929-40.
- Farrell, M.B., et al., SNMMI Procedure Standard/EANM Guideline for Gated Equilibrium Radionuclide Angiography. J Nucl Med Technol, 2020. 48(2): p. 126-135.
- 102. Ioannidis, J.P., T.A. Trikalinos, and P.G. Danias, Electrocardiogram-gated singlephoton emission computed tomography versus cardiac magnetic resonance imaging for the assessment of left ventricular volumes and ejection fraction: a meta-analysis. J Am Coll Cardiol, 2002. 39(12): p. 2059-68.
- 103. Einstein, A.J., et al., Radiation dose to patients from cardiac diagnostic imaging. Circulation, 2007. 116(11): p. 1290-305.
- 104. Einstein, A.J., et al., Multiple testing, cumulative radiation dose, and clinical indications in patients undergoing myocardial perfusion imaging. Jama, 2010. 304(19): p. 2137-44.
- Dencker, M., O. Björgell, and J. Hlebowicz, Effect of food intake on commonly used pulsed Doppler and tissue Doppler measurements. Echocardiography, 2011. 28(8): p. 843-7.
- 106. de Simone, G., et al., Assessment of left ventricular function by the midwall fractional shortening/end-systolic stress relation in human hypertension. J Am Coll Cardiol, 1994. 23(6): p. 1444-51.
- 107. Reichek, N., et al., Noninvasive determination of left ventricular end-systolic stress: validation of the method and initial application. Circulation, 1982. 65(1): p. 99-108.
- 108. Hlebowicz, J., et al., The effect of endogenously released glucose, insulin, glucagonlike peptide 1, ghrelin on cardiac output, heart rate, stroke volume, and blood pressure. Cardiovasc Ultrasound, 2011. 9: p. 43.
- 109. Nikolaidis, L.A., et al., Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation, 2004. 109(8): p. 962-5.
- Sokos, G.G., et al., Glucagon-like peptide-1 infusion improves left ventricular ejection fraction and functional status in patients with chronic heart failure. J Card Fail, 2006. 12(9): p. 694-9.
- 111. Nagaya, N., et al., Hemodynamic and hormonal effects of human ghrelin in healthy volunteers. Am J Physiol Regul Integr Comp Physiol, 2001. 280(5): p. R1483-7.

- Crepaz, R., et al., Age-related variations of left ventricular endocardial and midwall function in healthy infants, children, and adolescents. Ital Heart J, 2005. 6(8): p. 634-9.
- 113. Grossman, W., D. Jones, and L.P. McLaurin, Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest, 1975. 56(1): p. 56-64.
- 114. Mayet, J., et al., Midwall myocardial shortening in athletic left ventricular hypertrophy. Int J Cardiol, 2002. 86(2-3): p. 233-8.
- 115. Palmieri, V., et al., Left ventricular chamber and myocardial systolic function reserve in patients with type 1 diabetes mellitus: insight from traditional and Doppler tissue imaging echocardiography. J Am Soc Echocardiogr, 2006. 19(7): p. 848-56.
- 116. Quinones, M.A., et al., Echocardiographic determination of left ventricular stress-velocity relations. Circulation, 1975. 51(4): p. 689-700.
- 117. Slotwiner, D.J., et al., Relation of age to left ventricular function in clinically normal adults. Am J Cardiol, 1998. 82(5): p. 621-6.
- 118. Tei, C., et al., New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function--a study in normals and dilated cardiomyopathy. J Cardiol, 1995. 26(6): p. 357-66.
- Vancheri, F., S. Vancheri, and M.Y. Henein, Effect of Age on Left Ventricular Global Dyssynchrony in Asymptomatic Individuals: A Population Study. Echocardiography, 2016. 33(7): p. 977-83.
- 120. Burns, A.T., et al., Left ventricular strain and strain rate: characterization of the effect of load in human subjects. Eur J Echocardiogr, 2010. 11(3): p. 283-9.
- 121. Arnlöv, J., et al., Myocardial performance index, a Doppler-derived index of global left ventricular function, predicts congestive heart failure in elderly men. Eur Heart J, 2004. 25(24): p. 2220-5.
- 122. Arnlöv, J., et al., A Doppler-derived index of combined left ventricular systolic and diastolic function is an independent predictor of cardiovascular mortality in elderly men. Am Heart J, 2005. 149(5): p. 902-7.
- 123. Carluccio, E., et al., Improvement of myocardial performance (Tei) index closely reflects intrinsic improvement of cardiac function: assessment in revascularized hibernating myocardium. Echocardiography, 2012. 29(3): p. 298-306.
- 124. Escande, W., et al., Left ventricular myocardial performance index predicts poor outcome during COPD exacerbation. Int J Cardiol, 2014. 173(3): p. 575-9.
- 125. Flanagan, R., et al., Left ventricular myocardial performance index change for detection of acute cellular rejection in pediatric heart transplantation. Pediatr Transplant, 2013. 17(8): p. 782-6.
- 126. Frea, S., et al., Prognostic role of myocardial performance index on long-term survival after heart transplantation: a prospective study. Echocardiography, 2013. 30(9): p. 1033-41.
- 127. Hanedan Onan, S., et al., Evaluation of Cardiovascular Changes in Children with BAVs. Pediatr Cardiol, 2016. 37(3): p. 472-81.

- 128. Levent, E., et al., Usefulness of the myocardial performance index (MPI) for assessing ventricular function in obese pediatric patients. Turk J Pediatr, 2005. 47(1): p. 34-8.
- 129. Poulsen, S.H., et al., Serial changes and prognostic implications of a Doppler-derived index of combined left ventricular systolic and diastolic myocardial performance in acute myocardial infarction. Am J Cardiol, 2000. 85(1): p. 19-25.
- 130. Rao, M., et al., Left ventricular function during acute high-altitude exposure in a large group of healthy young Chinese men. PLoS One, 2015. 10(1): p. e0116936.
- Ruggiero, A., et al., Myocardial performance index and biochemical markers for early detection of doxorubicin-induced cardiotoxicity in children with acute lymphoblastic leukaemia. Int J Clin Oncol, 2013. 18(5): p. 927-33.
- 132. Tüzün, N., et al., TEI Index in elite sprinters and endurance athletes. J Sports Med Phys Fitness, 2015. 55(9): p. 988-94.
- 133. Lind, L., B. Andrén, and J. Arnlöv, The Doppler-derived myocardial performance index is determined by both left ventricular systolic and diastolic function as well as by afterload and left ventricular mass. Echocardiography, 2005. 22(3): p. 211-6.
- 134. Čelutkienė, J., et al., Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). Eur J Heart Fail, 2020. 22(9): p. 1504-1524.
- 135. Dencker, M. and M. Stagmo, Reported normal values and weighted means for commonly used echocardiography pulsed Doppler and tissue Doppler measurements. Clin Physiol Funct Imaging, 2018. 38(3): p. 341-350.
- 136. Adams, J.C., et al., Postprandial Hemodynamics in Hypertrophic Cardiomyopathy. Echocardiography, 2015. 32(11): p. 1614-20.
- 137. Gilligan, D.M., et al., Cardiovascular and hormonal responses to a meal in hypertrophic cardiomyopathy: a comparison of patients with and without postprandial exacerbation of symptoms. Clin Cardiol, 1996. 19(2): p. 129-35.
- 138. Cowie, B., et al., Measurement of Stroke Volume With Echocardiography Compared to Gold Standard Cardiac Magnetic Resonance Imaging: An Observational Study. J Cardiothorac Vasc Anesth, 2023. 37(9): p. 1639-1645.
- 139. Alam, M., et al., Acute effects of smoking on diastolic function in healthy participants: studies by conventional doppler echocardiography and doppler tissue imaging. J Am Soc Echocardiogr, 2002. 15(10 Pt 2): p. 1232-7.

# About the author



**Ylva Gårdinger** studied medicine at Lund University and graduated in 2004. After an internship in Kalmar she worked in different medical specialities, including cardiology and clinical physiology, and she has been a radiologist at Skåne University Hospital since 2016. She is also a dog owner and middle aged mother of two young children. When there is free time left, she spends it on wind music and reading mediocre literature.





Department of Translational Medicine

Lund University, Faculty of Medicine Doctoral Dissertation Series 2024:77 ISBN 978-91-8021-572-5 ISSN 1652-8220

