Heart Failure and Pancreas Exocrine Insufficiency

Dams, Olivier C.; Vijver, Marlene A. T.; van Veldhuisen, Charlotte L.; Verdonk, Robert C.; Besselink, Marc G.; van Veldhuisen, Dirk J.

Published in:
Journal of Clinical Medicine

DOI:
10.3390/jcm11144128

Publication date:
2022

Journal of
Clinical Medicine

MDPI

Review

Heart Failure and Pancreas Exocrine Insufficiency: Pathophysiological Mechanisms and Clinical Point of View

Olivier C. Dams [1,*], Marlene A. T. Vijver [1], Charlotte L. van Veldhuisen [2,3], Robert C. Verdonk [4], Marc G. Besselink [2,3] and Dirk J. van Veldhuisen [1]

[1] Department of Cardiology, University Medical Center Groningen, University of Groningen, 9700 RB Groningen, The Netherlands; m.a.t.vijver@umcg.nl (M.A.T.V.); d.j.van.veldhuisen@umcg.nl (D.J.v.V.)
[2] Department of Surgery, Amsterdam UMC, University of Amsterdam, 1100 DD Amsterdam, The Netherlands; c.l.vanveldhuisen@amsterdamumc.nl (C.L.v.V.); m.g.besselink@amsterdamumc.nl (M.G.B.)
[3] Amsterdam Gastroenterology Endocrinology Metabolism, 1100 DD Amsterdam, The Netherlands
[4] Department of Gastroenterology and Hepatology, St. Antonius Hospital, 3435 CM Nieuwegein, The Netherlands; r.verdonk@antoniusziekenhuis.nl
* Correspondence: o.c.dams@umcg.nl

Abstract: Heart failure is associated with decreased tissue perfusion and increased venous congestion that may result in organ dysfunction. This dysfunction has been investigated extensively for many organs, but data regarding pancreatic (exocrine) dysfunction are scarce. In the present review we will discuss the available data on the mechanisms of pancreatic damage, how heart failure can lead to exocrine dysfunction, and its clinical consequences. We will show that heart failure causes significant impairment of pancreatic exocrine function, particularly in the elderly, which may exacerbate the clinical syndrome of heart failure. In addition, pancreatic exocrine insufficiency may lead to further deterioration of cardiovascular disease and heart failure, thus constituting a true vicious circle. We aim to provide insight into the pathophysiological mechanisms that constitute this reciprocal relation. Finally, novel treatment options for pancreatic dysfunction in heart failure are discussed.

Keywords: heart failure; interactions; pancreatic exocrine insufficiency; cardiac cachexia; congestion; malnutrition

Citation: Dams, O.C.; Vijver, M.A.T.; van Veldhuisen, C.L.; Verdonk, R.C.; Besselink, M.G.; van Veldhuisen, D.J. Heart Failure and Pancreas Exocrine Insufficiency: Pathophysiological Mechanisms and Clinical Point of View. *J. Clin. Med.* **2022**, *11*, 4128. https://doi.org/10.3390/jcm11144128

Academic Editor: Andrea Frustaci

Received: 22 May 2022
Accepted: 14 July 2022
Published: 15 July 2022

1. Introduction

Heart failure is a complex clinical syndrome resulting from functional or structural disorders, leading to impaired ventricular filling or ejection of blood to the systemic circulation to meet metabolic requirements and accommodate venous return [1]. Heart failure is associated with decreased output (forward failure) and increased congestion (backward failure) that leads to disseminated organ dysfunction [2], which is generally associated with the severity of disease. Extensive work has been done in the field of dysfunction of the kidney [3,4], liver [5,6], the intestines and gut [7,8] and even the bone marrow [9], brain [10] and the placenta [11].

Pancreas function/dysfunction in heart failure has received little attention in the literature, which is somewhat surprising since malnutrition and gastrointestinal symptoms are common, as is dysfunctional insulin signaling [7,12,13]. The lack of research in this field may be related to the complexity of measuring pancreatic functioning and measuring the perfusion of human pancreatic tissue. Additionally, the pancreas has both an endocrine and exocrine function, and although there is significant interaction between the two systems, both are considered independent in functional testing.

Prior research has mostly been focused on the endocrine function of the pancreas in patients with heart failure, demonstrating impaired signaling and enhanced insulin clearance [14,15]. Heart failure is associated with an insulin resistant state, linked to the

overactivation of the sympathetic nervous system [13,14]. As the endocrine pancreas represents the minority of the organ volume [16] and is relatively resistant to disturbed hemodynamics [17], the present review will focus on the exocrine function of the pancreas, its associated changes in heart failure, the pathophysiological mechanisms, and lastly the clinical consequences.

2. Pancreatic Circulation and Hemodynamics

The position of the pancreatic gland in the abdominal cavity and its complex vascular anatomy means that pancreatic blood flow is difficult to measure accurately using non-invasive methods [18]. Blood flow to the pancreas approximates about 1% of the cardiac output in healthy adults [19]. Most of the supply to the pancreas body and tail is derived from the splenic artery, a branch of the celiac trunk [19,20]. The superior and inferior pancreaticoduodenal arteries supply the head and neck of the pancreas. The superior pancreaticoduodenal artery branches from the gastroduodenal artery, which in turn branches from the common hepatic artery. The inferior pancreaticoduodenal artery is an early branch of the superior mesenteric artery. These two arteries thus represent an anastomosis between the celiac and mesenteric systems [20], which, similar to the cerebral circulation, allows for maintenance of pancreatic blood flow when vascular integrity is compromised. The venous drainage of the pancreas is entirely to the portal system through the splenic and superior mesenteric veins.

The healthy pancreas is capable of intrinsic regulation of blood flow by myogenic and metabolic regulatory mechanisms [21]. As a result of either reduced arterial pressure or elevated venous pressure, the pancreas increases capillary exchange capacity and is able to maintain oxygen extraction [21]. Additionally, reductions in arterial pressure stimulate autoregulation (e.g., decrease in vascular resistance) to allow for maintenance of sufficient blood flow [21]. Elevations in venous pressure are maintained solely by increased oxygen extraction, and lack of compensatory autoregulatory mechanisms. As has also been demonstrated in animal models, when venous (portal) pressures increase beyond specific thresholds, pancreatic blood flow is reduced [22].

The splanchnic veins are characterized by a much higher compliance and a large proportion of the circulating blood volume [23], hence they act as a venous reservoir [24]. Recently, modulation of this system has received attention as a treatment target in acute heart failure [25,26]. One of the hallmarks of the splanchnic vascular system, specifically the veins, is the large number of adrenergic receptors [27], allowing for a more pronounced vasomotor response. This allows for rapid fluid shifts to buffer changes in circulatory volume. The shift of blood from the splanchnic to the central compartment is capable of further increasing cardiac filling pressures and exacerbating decompensation. In case of expanded intravascular volume, the compliance of the splanchnic veins is decreased; when combined with pronounced venoconstriction due to strong adrenergic response, this renders the organs in the abdominal compartment, including the pancreas, prone to congestion (Figure 1B).

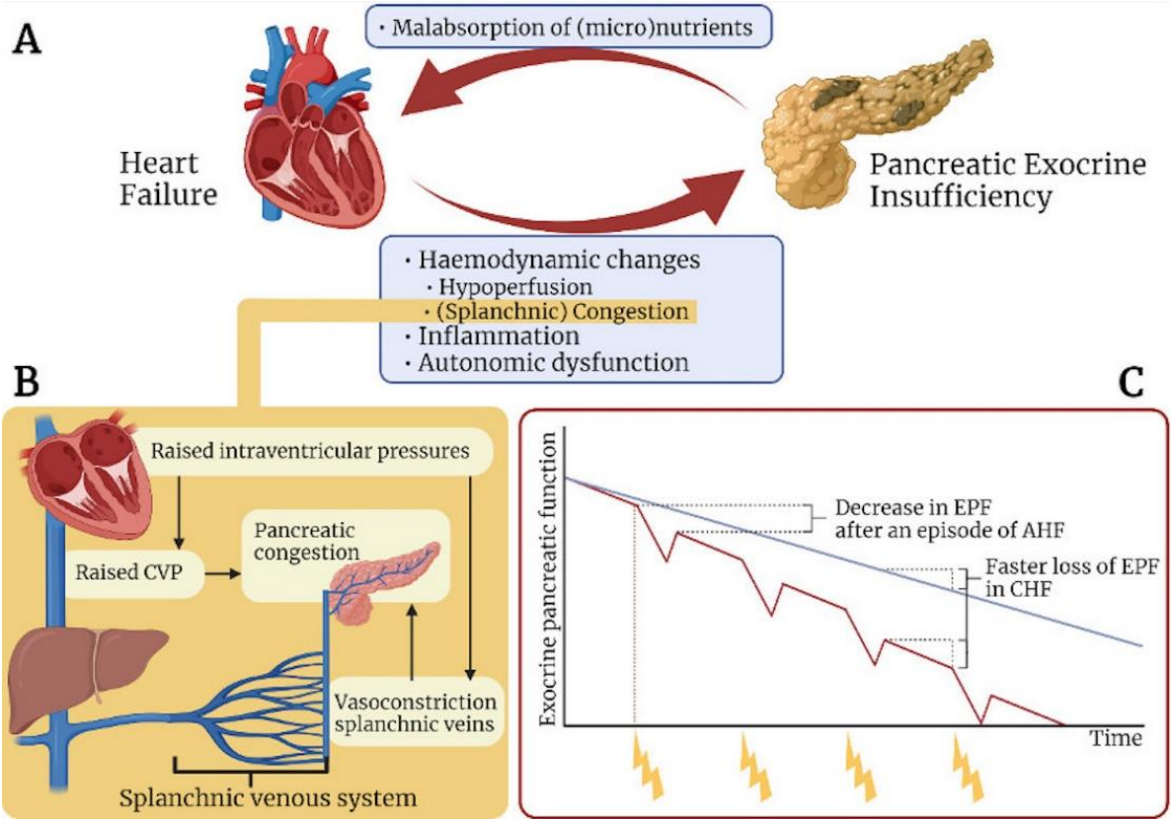

Figure 1. (**A**) Possible interactions between heart and pancreas. Several factors are hypothesized to affect the pancreatic exo-crine tissue in heart failure. This is mainly due to ischemic injury and congestion, leading to necrosis of acinar cells. As a result, EPF is suggested to decrease, followed by malabsorption of nutrients, which further deteriorates heart failure. (**B**) Schematic view of the venous system affected by heart failure. Due to decreased organ perfusion, the venous splanchnic system contracts, aiming to increase the circulatory volume. Together with raised CVP, these mecha-nisms are believed to lead to compromised venous drainage of the pancreas, resulting in congestion. (**C**) Graph showing the proposed loss of EPF in the normal situation compared to patients with heart failure. Every episode of AHF can be seen as a new attack on the pancreatic exocrine tissue. Repetitive hits, in combination with chronic heart failure, is hypothesized to result in exocrine pancreatic insufficiency.

3. Pancreatic Structure and Function/Dysfunction

The pancreas is a dual-functional gland, performing both endocrine and exocrine functions. The endocrine functions are performed through the islets of Langerhans, which represent 1% of the pancreas and consist of hormone-secreting cells dispersed throughout and between the exocrine tissue. The islets are well-vascularized and secrete hormones, such as insulin, glucagon, somatostatin, ghrelin and pancreatic polypeptide [28], which act to maintain glucose homeostasis and regulate digestion. More than 95% of the pancreas is composed of exocrine tissue, consisting of acinar and ductal cells, which produce and discharge digestive enzymes and bicarbonate respectively into a system of intercalated ducts emptying into the proximal duodenum, allowing for digestion of lipids, carbohydrates and protein [29].

The regulation of exocrine pancreatic secretions involves a complex interplay of hormonal-hormonal and neurohormonal interactions [30]. The pancreas is extensively supplied with nerve fibers, nerve trunks and ganglia scattered throughout the tissue. The autonomic nervous system regulates pancreatic endocrine and exocrine secretions [31], especially the efferent parasympathetic pathways, consisting of the vagal central dorsal motor nucleus and pancreatic neurons, profoundly stimulate exocrine secretions [32]. The

principal stimulatory hormones are cholecystokinin (CCK) and secretin; both of which are regulated by several feedback mechanisms [33]. Secretin, for example, is released primarily in response to increased acidity in the duodenum and stimulates the release of bicarbonate by ductal cells. CCK is released from endocrine cells in the gut by the presence of lipids and proteins, and acts through vagal afferents to stimulate the functional units of the exocrine pancreas—the acinar cells.

Pancreatic Exocrine Insufficiency

Pancreatic enzymes play a key role in the digestion of macronutrients and absorption of micronutrients. Due to a variety of (structural) diseases, pancreatic exocrine insufficiency may occur. The most common definition of pancreatic exocrine insufficiency is "a reduction of pancreatic exocrine activity in the intestine at a level that prevents normal digestion" [34]. The pathophysiology underlying the development of exocrine insufficiency is complex, and three distinct mechanisms can be implicated [35]:

- Injury to pancreatic exocrine parenchyma, resulting in reduced synthetic capacity (e.g., [recurrent] pancreatitis, cystic fibrosis, ageing)
- Reduced stimulation of pancreatic enzyme production (e.g., celiac disease, autonomic dysfunction)
- Pancreatic duct obstruction (e.g., malignancy)

In the case of generalized inflammation and malnutrition, exocrine secretions are decreased. Pancreatic exocrine insufficiency (PEI) is therefore seen in the wasting syndrome of, for example, chronic renal disease [36] and the critically ill [37]. It has previously been demonstrated that the presence of exocrine pancreatic insufficiency is associated with survival [38,39]. The main clinical consequence of (untreated) pancreatic exocrine insufficiency is maldigestion and subsequent malnutrition. In particular, the maldigestion of lipids may occur, resulting in deficiencies of fat-soluble vitamins (A, D, E, K) and minerals (e.g., copper, selenium, zinc) [34,40]. These deficiencies may cause downstream organ or immune dysfunction.

Pancreatic exocrine function is difficult to assess because of the inaccessibility of the gland's secretions. Functional tests are either based on the measurement of secreted enzymes and bicarbonate (direct tests), or the investigation of secondary effects that are due to the lack of enzymes (indirect tests) (Table 1) [34]. Indirect tests are easy to administer, cheap, but generally less sensitive and particularly less-specific. The most employed test is the determination of fecal elastase-1 (FE-1), a pancreatic exocrine-specific enzyme that is not degraded in the bowel lumen [34]. This test requires a single stool collection, is easy to administer, cheap, and has demonstrated good diagnostic accuracy [41]. Alternatively, direct tests involve the collection of exocrine secretions through duodenal intubation [34]. These tests are more sensitive and specific, but their costs and invasive nature limits their routine use in clinical practice. Given the complexity of diagnosis, it is recommended that the evaluation of exocrine insufficiency is based on the assessment of the patient's history and clinical state, weight-loss and nutritional status combined with functional testing [34].

In principle, pancreatic exocrine insufficiency is a manageable condition. The aim of treatment of exocrine insufficiency is to eliminate malabsorption and maldigestion and to normalize the nutritional state. The cornerstone of treatment is pancreatic enzyme replacement therapy (PERT) [34]. PERT involves oral administration of enzyme preparations and has been shown to improve outcomes [42–44] in both malignant and benign conditions associated with exocrine dysfunction.

Table 1. Diagnostic tools of measuring pancreatic exocrine insufficiency.

Test	Advantages	Disadvantages
	Non-invasive	
Fecal elastase-1 (FE-1) single stool measurement	• Easy to determine • Low patient burden • Cheap	• Low accuracy in mild to moderate PEI • Frequent false positives • Not accurate in case of diarrhea
Coefficient of fat absorption (CFA) 3-day stool collection	• High accuracy, former gold-standard	• Requires 3-day stool collection and 5-day strict diet
13C-mixed triglyceride breath test	• Can be used for treatment monitoring	• Not completely validated and no agreement on protocol • Limited availability • Time consuming (6 h)
Trial of PERT Pancreatic Enzyme Replacement Therapy	• Also possible treatment • Low patient burden	• Only in symptomatic patients, clinically highly suspected • Risk of over- and under diagnosis
	Invasive	
CCK-stimulated pancreatic function test measuring enzyme secretion acinar cells in duodenum	• Most direct measure of enzyme secretion • Accuracy for detecting mild/moderate insufficiency	• Duodenal intubation • Long procedure (2 h) • Expensive • High patient burden
Secretin stimulated pancreatic function test measuring HCO_3^- and fluid secretion ductal cells in duodenum	• Most direct measure of HCO_3^- and fluid secretion • Accuracy for detecting mild/moderate insufficiency	• Duodenal intubation • Long procedure (2 h) • Expensive • High patient burden
Secretin—CCK test, combination of the above		
	Imaging	
• **Endoscopic retrograde cholangiopancreatography** • **Computed tomography** • **Endoscopic ultrasound** • **Magnetic resonance imaging**	• Identify structural abnormalities (ductal changes, hyperechoic regions, cysts, parenchymal lobularity, calcifications)	• Poor sensitivity for mild disease • Evaluates probability of PEI in chronic pancreatitis

CCK—cholecystokinin.

4. Studies on Pancreatic Injury in Heart Failure

In heart failure, a combination of contributors, such as low cardiac output, activation of the renin-angiotensin-aldosterone system, and natriuretic peptide axes, and the sympatho-sympathetic reflex lead to tissue injury mainly through hypoperfusion and/ or congestion [1]. Herein we summarize the few prior studies on pancreatic involvement in animal and human models of heart failure and cardiac dysfunction.

Acute pancreatic injury has been well described in earlier studies in the setting of cardiac surgery [45–51]. In this population, post-operative biochemical derangement (hyperamylasemia/hyperlipasemia) is prevalent, detected in nearly one third of patients [47]. Additionally, hemodynamic factors, such as hypotension, low cardiac output, and increased bypass time, are independent predictors [47]. Although the presentation is usually subtle, severe (fulminating) pancreatitis has been documented in some patients [45,46,48,51,52]. The development of ischemic pancreatitis is associated with microvascular impairment and stasis, formation of thrombi, release of digestive enzymes and inflammation [53,54]. In severe cases, this proceeds to systemic inflammation leading to systemic inflammatory response syndrome and multi-organ involvement, an infrequent but well-recognized, severe, complication of cardiac surgery, termed post-pump pancreatitis.

In (acute) heart failure induced by rapid ventricular pacing in dogs, pancreatic perfusion declines rapidly, even before significant limitations in renal blood flow are seen [55]. Older studies in humans already demonstrated that in cases of acute cardiogenic shock, the

incidence of pancreatic injury is 50–55% in those with acute tubular necrosis and 9% in those without [56]. The disproportional decline in pancreatic perfusion is also confirmed by an earlier animal study [57], utilizing a pig-model of cardiogenic shock induced by pericardial tamponade. This study showed a rapid, highly disproportional, reduction in pancreatic perfusion and increase in vascular resistance. Interestingly, this disproportionality is partially reversible with pharmacological renin-angiotensin inhibition [57]. Histopathological follow-up analyses of pancreatic tissue in the abovementioned dog model demonstrated atrophy of the acinar cells specifically [58,59], indicating that an association between the hemodynamic perturbations of heart failure and loss of exocrine parenchyma exists.

The interaction between the abdominal compartment and central hemodynamics, inflammation, malnutrition and catabolism has been established previously in several studies in patients with cardiac cachexia. Gut hormones, such as leptin and ghrelin, are elevated in cachectic patients [60,61], a finding that is thought to reflect the anabolic/catabolic imbalance. A recent prospective study in an advanced heart failure population demonstrated that the endocrine peptide somatostatin, expressed in the stomach, small intestine and pancreas, and a potent inhibitor of pancreatic hormones and exocrine secretions, is elevated in chronic heart failure and independently related to right-sided filling pressures and cardiac index [62]. Cardiac cachexia itself is also strongly associated with right-sided filling pressures [7]; the elevated intestinal hormones, such as somatostatin, could thus reflect the pathologic hormonal milieu, but also the effect of congestion on the abdominal compartment.

Only three relatively small studies evaluated pancreatic function in the human heart failure population [63–65]. The largest, most recent, study examined FE-1 in 104 patients with mostly mild heart failure [65] and showed that 56% of these patients had evidence for exocrine insufficiency (FE-1 < 200 μg/g), which appeared to be associated with both gastrointestinal symptoms and the severity of heart failure. The high prevalence of pancreatic exocrine insufficiency was also found in an earlier Turkish report [64]. This study, in 52 patients with mild and moderate heart failure and 31 healthy controls, also showed a high prevalence of pancreatic exocrine insufficiency (70%) in severe heart failure, and strong associations between FE-1 and cachexia/malnourishment and exocrine insufficiency. In a third study, Vujasinovic et al. [63] provided evidence for decreased circulating fat-soluble vitamins/micronutrients, particularly vitamin D, in all patients with heart failure and pancreatic exocrine insufficiency. Although these three studies are important, only little information on patient selection, baseline characteristics, and etiology was provided, and it appears that a relatively mild heart failure population was examined, based on natriuretic peptides and echocardiography. Nonetheless, these studies support the concept that heart failure is associated with pancreatic exocrine insufficiency.

5. Mechanisms of Pancreatic Damage in Heart Failure

Almost a century ago, it was first hypothesized that repetitive attacks of acute pancreatitis progressed to chronic pancreatitis [66]. The hallmark of chronic pancreatitis is the progressive, fibrotic destruction of tissue, resulting from a combination of (genetic) susceptibility and incremental damage from a repetitive injury. In contrast to other organs, such as the skin, liver and intestines, but similar to the heart, the adult pancreas displays a limited capacity to regenerate [67,68] and a tendency towards fibrogenesis and cellular atrophy in response to injury. Although acinar cells increase their division rate after injury [69,70], tissue mass is only partially restored, allowing for the development of exocrine insufficiency. The suggested mechanisms of pancreatic dysfunction resulting in exocrine insufficiency in heart failure are discussed in this chapter and depicted in Figure 2.

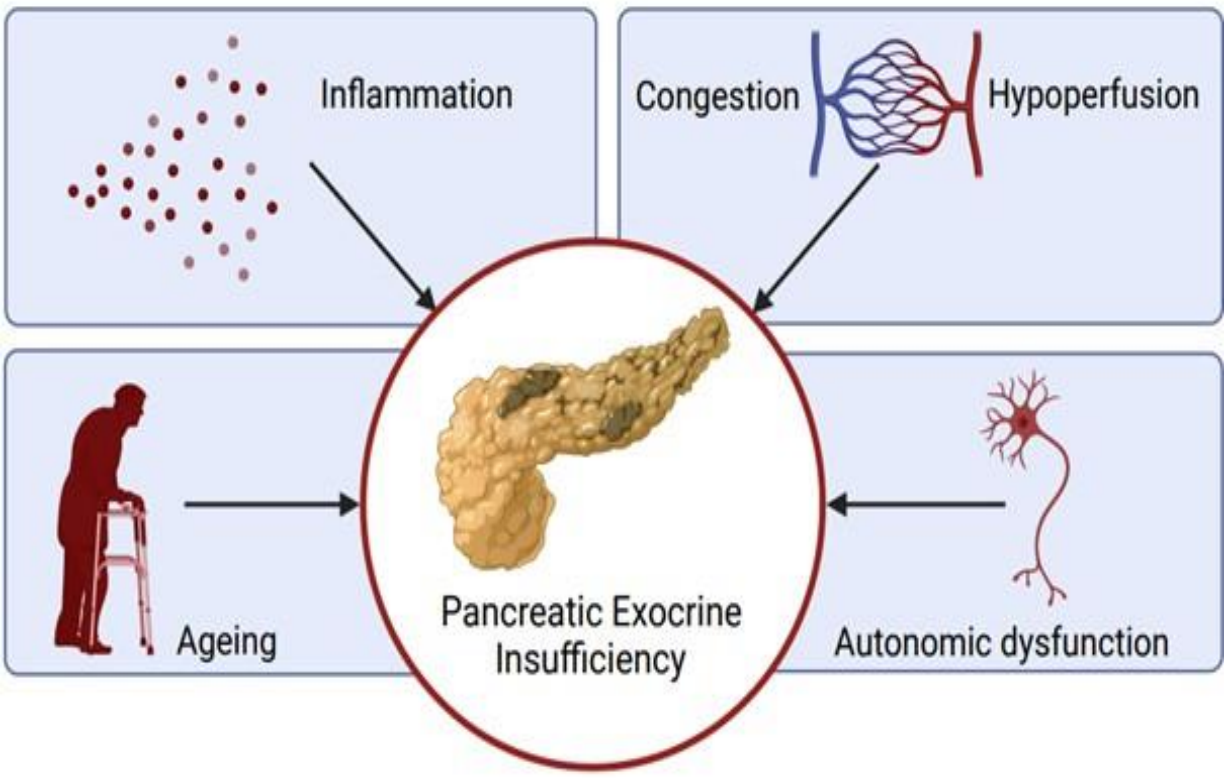

Figure 2. Proposed mechanisms of pancreatic damage in heart failure. Several factors have been identified that possibly damaged the exocrine pancreatic tissue in patients with heart failure. We know that in healthy individuals, pancreatic exocrine insufficiency can develop over time. In patients with heart failure, the pancreas is supposedly affected by deranged hemodynamics (e.g., congestion and hypoperfusion), chronic low-grade inflammation and autonomic dysfunction, therefore possibly accelerating the development of pancreatic exocrine insufficiency. Figure created with BioRender.com (accessed on 13 May 2022).

5.1. Ageing

Across the human lifespan, pancreatic structure and function changes: volume decreases, ducts dilate, and exocrine function gradually decreases [71]. Similar to other abdominal organs, such as the liver [72], there is an age-dependent decline in perfusion [73], which contributes to gradual atrophy of acinar cells and eventually (sub-clinical) exocrine insufficiency. This process appears to develop independent of co-morbidities. Prior studies in healthy individuals showed that age correlates with exocrine secretions and more than one fifth of healthy older adults exhibit pancreatic exocrine insufficiency [74,75]. It can be hypothesized that repetitive hits of accumulating hypoperfusion in heart failure accelerate the changes seen in ageing, putting patients at increasing risk for (premature) development of exocrine dysfunction (Figure 1C).

5.2. Hemodynamics

The pancreas is vulnerable to ischemic injury, a factor that plays an important role in the development of a wide range of pancreatic disease, particularly pancreatitis [76–78]. Ischemic injury occurs rapidly with subsequent induction of a significant inflammatory response and acinar cell injury [77,79]. The functional consequences of temporary ischemic damage on the exocrine pancreas are unknown, as studies on tissue regeneration after recovery from ischemic injury humans are scarce [29]. Older data from autopsy studies on patients with ischemic pancreatic injury [59] demonstrated that a wide range of histopathological changes occur, especially in the acini. Peripheral acinar atrophy, as already described more than 35 years ago by Takahashi et al., is found exclusively in con-

gestive heart failure, with more than 10% of patients exhibiting this finding at autopsy [59]. Similar histological changes are seen in models of ischemia related to atherosclerosis in ageing or long-standing hypoperfusion [71,77]. These data suggest that chronic ischemic injury damages the functional unit of the exocrine pancreas - the acinus.

Under conditions of acute heart failure manifesting as cardiogenic shock, there is systemic vasoconstriction to maintain effective circulation. This response is disproportionate in the mesenteric circulation. Although the sympathetic nervous system mediates vasoconstriction, the predominant cause of this disproportionate response in the mesenteric circulation seems to be the renin-angiotensin axis [57,80,81]. The mesenteric vascular smooth muscle has a disproportionate affinity for angiotensin II [82]. A local renin-angiotensin system is also present in the pancreas, a feature that can further amplify oxidative stress and tissue injury [83,84]. This renders the pancreas susceptible to injury in heart failure, where renin-angiotensin overactivation is a central feature underlying the pathophysiology.

In (advanced) heart failure, the abdominal compartment is subjected to progressive and persistent volume overload, a factor that compromises oxygen supply and independently predicts outcome and the development of cardiac cachexia [5,7,12]. Fluid overload or high (right) ventricular filling pressures, and elevated central venous pressure, are transmitted directly to the hepatic veins and sinusoidal beds in the liver [85]. This results in sinusoidal congestion and peri-sinusoidal edema, decreasing the oxygen diffusion of hepatocytes. Due to their close interaction and coupling, where venous drainage of the pancreas occurs entirely through the portal system, the presence of acute liver injury itself puts patients at risk of pancreatic injury. Portal hypertension has been shown to cause fibrosis and damage the intima of the pancreatic vein wall, resulting in impaired drainage of blood flow [86,87]. Given its anatomical position and complex auto-regulation [22], we hypothesize congestive pancreatopathy is a common, unrecognized, clinical entity in patients with heart failure.

5.3. Inflammation

Inflammatory processes of the pancreas are a well-known clinical entity [88]. Acute pancreatitis is driven by a local and systemic inflammatory cascade, resulting in tissue atrophy and fibrosis [89,90]. The disease seems to be triggered by inappropriate activation of pancreatic enzymes and subsequent auto-digestion [91]. Damage is enhanced by a sterile inflammatory response consisting of the activation of transcription factors, such as NF-κB [90,92], cytokine dysregulation [93,94] and eventually recruitment of macrophages and T cells [95,96]. It is unknown whether a single attack of acute pancreatitis has significant (long-term) effects on exocrine function. Animal studies demonstrated that exocrine function is decreased during acute pancreatitis [97–99]. Studies in humans showed a high prevalence of exocrine insufficiency after recovery from acute pancreatitis (27.1%), with a higher prevalence in more severe disease [100,101].

Persistent (low-grade) sterile inflammation also represents an important pathogenic mechanism in heart failure, which seems to be unresponsive to treatment [102,103] and correlates with severity of disease [104] and the development of cardiac cachexia. Elevated inflammatory biomarkers are a hallmark feature of heart failure and thought to be both cause and consequence of disease progression. Additionally, several other associated conditions, such as atrial fibrillation [105], coronary artery disease [106], and anemia [107], are to some extent driven by inflammation. This inflammatory state is associated with end-organ dysfunction through direct tissue damage, impairment of extracellular matrix networks, and alterations in metabolism and endocrine signaling [108,109]. It is hypothesized that chronic (low-grade) inflammation in heart failure facilitates damage to the exocrine pancreas parenchyma.

5.4. Autonomic Dysfunction

Heart failure is characterized by marked autonomic dysfunction, i.e., increased sympathetic activation (and circulating catecholamines) on the one hand, and reduced vagal (or

parasympathetic) activity on the other [110,111]. This disturbed autonomic balance can be (partly) corrected by drug treatment [112]. Interestingly, baroreflex sensitivity at baseline is reduced in patients with heart failure but is unaffected by unloading the cardiopulmonary baroreceptors (through lower body negative pressure application) [113], suggesting that chronic overstimulation leads to insensitivity of the autonomic nervous system.

The autonomic nervous system also plays a role in the regulation of pancreatic exocrine and endocrine function and the secretion of enzymes [28]. Indeed, cholecystokinin stimulates pancreatic exocrine secretion through vagal neurons, and so it is conceivable that in heart failure a chronic reduction of parasympathetic activation and overstimulation of the sympathetic nervous system may lead to insensitivity of the entero-pancreatic reflexes, similar to what is described above, thus causing pancreatic exocrine insufficiency [113,114]. Interestingly, in patients with diabetes mellitus, a condition that is also common in patients with heart failure, reduced exocrine stimulation is also observed, which may be the result of reduced parasympathetic activity [115]. Studies will be needed to investigate the effects on vagal stimulation on pancreatic enzyme secretion and function, in patients with heart failure versus those without, to investigate whether the pancreas in heart failure may also be less responsive to vagal stimulation.

6. Summary and Clinical Implications

The aim of this review is to focus on the exocrine function of the pancreas, its associated changes in heart failure and the pathophysiological mechanisms. Although only three previous reports have directly addressed the relationship between heart failure and exocrine insufficiency using direct clinical markers (e.g., FE-1), the various studies discussed in this review showed that several of the hallmarks and consequences of heart failure, such as abnormal hemodynamics and repetitive tissue injury, autonomic dysfunction and systemic inflammation, provide a detrimental environment capable of damaging specifically pancreatic exocrine tissue. A two-hit model in which (1) ongoing/chronic hemodynamic injury and inflammation leading to acinar atrophy and (2) impaired tissue stimulation subsequent to autonomic dysfunction is proposed (Figure 1A). It is hypothesized that this condition leads to further clinical deterioration by accelerating wasting and malnutrition. Although it is reasonable that these pathological mechanisms are capable of disproportionally damaging pancreatic tissue, the development of pancreatic insufficiency as heart failure worsens is still unclear. Based on prior data from studies on organ dysfunction in heart failure, one can assume a progressive trend related to heart failure severity, but this is certainly partly hypothetical. Future (longitudinal) studies in both mild and advanced heart failure populations are therefore encouraged.

Patients with severe (advanced) heart failure may develop cardiac cachexia, which is a strong independent prognostic factor [116] that intensifies the pathological cardiac remodeling process [117]. The pathogenesis of cardiac cachexia is complex and involves systemic dysregulation of inflammatory and metabolic pathways. Pancreatic exocrine insufficiency may be both a contributor and a consequence of cardiac cachexia. Several features of cardiac cachexia, such as abdominal congestion, inflammation and sympathetic overactivation [7,12,118,119], overlap with potential mechanisms of pancreatic injury. Alternatively, pancreatic exocrine insufficiency can also (further) exacerbate cardiac cachexia. Muscle wasting and (protein) malnutrition, for example, are common in heart failure [120], but could also be related to pancreatic exocrine insufficiency. This insufficiency may be treatable, thus making it a potential element of heart failure and cardiac cachexia that is amenable to intervention. Larger observational studies addressing the prevalence of pancreas exocrine insufficiency in patients with heart failure are needed to determine which patients are affected most. We encourage other researchers to identify patient characteristics and risk factors for developing pancreatic disease, therewith possibly providing new options for prevention or treatment. Finally, supplemental therapies (PERT) could be further explored in patients with pancreas dysfunction and heart failure.

In addition to aggravating the wasting of advanced heart failure, pancreatic exocrine insufficiency may result in micronutrient deficiencies subsequent to maldigestion of lipids. In particular, deficiencies in several fat-soluble minerals, such as selenium and zinc, may occur [121]. These micronutrients are essential for cardiac mitochondrial function and oxidative stress response, and their presence is associated with positive outcomes in heart failure [122]. Furthermore, reduced circulating fat-soluble vitamins may further deteriorate the clinical status in heart failure. Vitamin D deficiency, for example, aggravates the wasting of cardiac cachexia by compromising bone mineral density. Additionally, vitamin D plays a significant role in cardiovascular homeostasis and remodeling, and prior studies showed that vitamin D deficiency is associated with cardiovascular events and negative outcomes in heart failure [123–127]. Studies that tested supplementation of vitamin D in heart failure have shown that this treatment reduces renal activity [128], but it does not improve outcomes in heart failure [129]. The exact reasons why this treatment is not beneficial over the long-term is unknown [130]. Interestingly, vitamin D supplementation also does not affect bone turnover [131], a finding that could be partially explained by dysfunctional vitamin D handling subsequent to (persistent) exocrine pancreatic dysfunction. Lastly, deficiencies of vitamins A, E and K reduce physical functioning by causing visual impairment, neurological symptoms and coagulopathy [40]. We encourage future trials that investigate supplementation of these minerals and vitamins in heart failure to also consider exocrine pancreatic function.

7. Conclusions

Although extensive work has been done on organ dysfunction in heart failure, the pancreas remains largely understudied. This review presents the pathophysiological mechanisms and available data that together suggest heart failure is associated with pancreatic exocrine insufficiency, a feature that can further deteriorate clinical status through malnutrition and maldigestion. As pancreatic exocrine insufficiency is a treatable, largely unrecognized condition, further research evaluating its prevalence and treatment in heart failure is encouraged.

Author Contributions: Conceptualization: O.C.D., M.A.T.V. and D.J.v.V. Investigation lead: O.C.D., investigation equal, M.A.T.V., C.L.v.V., R.C.V., M.G.B. and D.J.v.V. Methodology lead: D.J.v.V., methodology equal, O.C.D., M.A.T.V., C.L.v.V., R.C.V. and M.G.B. Writing—original draft lead: O.C.D., equal, M.A.T.V. and D.J.v.V. Writing—review & editing lead: O.C.D., equal, M.A.T.V., C.L.v.V., R.C.V., M.G.B. and D.J.v.V. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. McDonagh, T.A.; Metra, M.; Adamo, M.; Gardner, R.S.; Baumbach, A.; Böhm, M.; Burri, H.; Butler, J.; Čelutkienė, J.; Chioncel, O.; et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **2021**, *42*, 3599–3726. [CrossRef] [PubMed]
2. Harjola, V.P.; Mullens, W.; Banaszewski, M.; Bauersachs, J.; Brunner-La Rocca, H.P.; Chioncel, O.; Collins, S.P.; Doehner, W.; Filippatos, G.S.; Flammer, A.J.; et al. Organ dysfunction, injury and failure in acute heart failure, from patho-physiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure As-sociation (HFA) of the European Society of Cardiology (ESC). *Eur. J. Heart Fail.* **2017**, *19*, 821–836. [CrossRef] [PubMed]
3. Damman, K.; van Deursen, V.M.; Navis, G.; Voors, A.A.; van Veldhuisen, D.J.; Hillege, H.L. Increased Central Venous Pres-sure Is Associated with Impaired Renal Function and Mortality in a Broad Spectrum of Patients with Cardiovascular Disease. *J. Am. Coll. Cardiol.* **2009**, *53*, 582–588. [CrossRef] [PubMed]
4. Boorsma, E.M.; ter Maaten, J.M.; Voors, A.A.; van Veldhuisen, D.J. Renal Compression in Heart Failure, The Renal Tam-ponade Hypothesis. *J. Am. Coll. Cardiol.* **2022**, *10*, 175–183.

5. Sundaram, V.; Fang, J.C. Gastrointestinal and Liver Issues in Heart Failure. *Circulation* **2016**, *133*, 1696–1703. [CrossRef]
6. Van Deursen, V.M.; Damman, K.; Hillege, H.L.; van Beek, A.P.; Van Veldhuisen, D.J.; Voors, A.A. Abnormal Liver Function in Relation to Hemodynamic Profile in Heart Failure Patients. *J. Card. Fail.* **2010**, *16*, 84–90. [CrossRef]
7. Valentova, M.; Von Haehling, S.; Bauditz, J.; Doehner, W.; Ebner, N.; Bekfani, T.; Elsner, S.; Sliziuk, V.; Scherbakov, N.; Murín, J.; et al. Intestinal congestion and right ventricular dysfunction: A link with appetite loss, inflammation, and cachexia in chronic heart failure. *Eur. Heart J.* **2016**, *37*, 1684–1691. [CrossRef]
8. Sandek, A.; Bauditz, J.; Swidsinski, A.; Buhner, S.; Weber-Eibel, J.; von Haehling, S.; Schroedl, W.; Karhausen, T.; Doehner, W.; Rauchhaus, M.; et al. Altered Intestinal Function in Patients with Chronic Heart Failure. *J. Am. Coll. Cardiol.* **2007**, *50*, 1561–1569. [CrossRef]
9. Westenbrink, B.D.; Voors, A.A.; De Boer, R.A.; Schuringa, J.J.; Klinkenberg, T.; Van Der Harst, P.; Vellenga, E.; Van Veldhuisen, D.J.; Van Gilst, W.H. Bone marrow dysfunction in chronic heart failure patients. *Eur. J. Heart Fail.* **2010**, *12*, 676–684. [CrossRef]
10. Erkelens, C.D.; van der Wal, H.H.; de Jong, B.M.; Elting, J.W.; Renken, R.; Gerritsen, M.; van Laar, P.J.; van Deursen, V.M.; van der Meer, P.; van Veldhuisen, D.J.; et al. Dynamics of cerebral blood flow in patients with mild non-ischaemic heart failure. *Eur. J. Heart Fail.* **2017**, *19*, 261–268. [CrossRef]
11. Siegmund, A.S.; Pieper, P.G.; Bilardo, C.M.; Gordijn, S.J.; Khong, T.Y.; Gyselaers, W.; van Veldhuisen, D.J.; Dickinson, M.G. Cardiovascular Determinants of Impaired Placental Function in Women with Cardiac Dysfunction. *Am. Heart J.* **2021**. [CrossRef] [PubMed]
12. Verbrugge, F.H.; Dupont, M.; Steels, P.; Grieten, L.; Malbrain, M.; Tang, W.W.; Mullens, W. Abdominal Contributions to Cardiorenal Dysfunction in Congestive Heart Failure. *J. Am. Coll. Cardiol.* **2013**, *62*, 485–495. [CrossRef] [PubMed]
13. Swan, J.W.; Walton, C.; Godsland, I.F.; Clark, A.L.; Coats, A.J.S.; Oliver, M.F. Insulin resistance in chronic heart failure. *Eur. Heart J.* **1994**, *15*, 1528–1532. [CrossRef] [PubMed]
14. Riehle, C.; Abel, E.D. Insulin Signaling and Heart Failure. *Circ. Res.* **2016**, *118*, 1151–1169. [CrossRef] [PubMed]
15. Melenovsky, V.; Benes, J.; Franekova, J.; Kovar, J.; Borlaug, B.A.; Segetova, M.; Tura, A.; Pelikanova, T. Glucose homeostasis, pancreatic endocrine function, and outcomes in ad-vanced heart failure. *J. Am. Heart Assoc.* **2017**, *6*, e005290. [CrossRef]
16. Isaacson, A.; Spagnoli, F.M. Pancreatic cell fate specification: Insights into developmental mechanisms and their application for lineage reprogramming. *Curr. Opin. Genet. Dev.* **2021**, *70*, 32–39. [CrossRef]
17. Vollmar, B.; Janata, J.; Yamauchi, J.; Wolf, B.; Heuser, M.; Menger, M.D. Exocrine, but not endocrine, tissue is susceptible to microvascular ischemia/reperfusion injury following pancreas transplantation in the rat. *Transpl. Int.* **1999**, *12*, 50–55. [CrossRef]
18. Machens, H.G.; Senninger, N.; Runkel, N.; Frank, G.; Von Kummer, R.; Herfarth, C. Advantages and disadvantages of using the hydrogen clearance technique to measure pancreatic blood flow. *Eur. J. Surg.* **1992**, *158*, 113–116.
19. Lewis, M.P.N.; Reber, H.; Ashley, S. Pancreatic Blood Flow and Its Role in the Pathophysiology of Pancreatitis. *J. Surg. Res.* **1998**, *75*, 81–89. [CrossRef]
20. Parks, D.A.; Jacobson, E.D. Physiology of the Splanchnic Circulation. *Arch. Intern. Med.* **1985**, *145*, 1278–1281. [CrossRef]
21. Kvietys, P.R.; McLendon, J.M.; Bulkley, G.B.; A Perry, M.; Granger, D.N. Pancreatic circulation: Intrinsic regulation. *Am. J. Physiol. Content* **1982**, *242*. [CrossRef] [PubMed]
22. Widdison, A.L.; Karanjia, N.D.; A Reber, H. Pancreatic vascular regulation in chronic pancreatitis in cats. *Gut* **1995**, *36*, 133–136. [CrossRef] [PubMed]
23. Hainsworth, R. The Importance of Vascular Capacitance in Cardiovascular Control. *Physiology* **1990**, *5*, 250–254. [CrossRef]
24. Gelman, S.; Warner, D.S.; Warner, M.A. Venous Function and Central Venous Pressure. *Anesthesiology* **2008**, *108*, 735–748. [CrossRef]
25. Fudim, M.; Jones, W.S.; Boortz-Marx, R.L.; Ganesh, A.; Green, C.L.; Hernandez, A.F.; Patel, M.R. Splanchnic Nerve Block for Acute Heart Failure. *Circulation* **2018**, *138*, 951–953. [CrossRef]
26. Fudim, M.; Patel, M.R.; Boortz-Marx, R.; Borlaug, B.A.; DeVore, A.D.; Ganesh, A.; Green, C.L.; Lopes, R.D.; Mentz, R.J.; Patel, C.B.; et al. Splanchnic Nerve Block Mediated Changes in Stressed Blood Volume in Heart Fail. *J. Am. Coll. Cardiol.* **2021**, *9*, 293–300.
27. Birch, D.J.; Turmaine, M.; Boulos, P.B.; Burnstock, G. Sympathetic Innervation of Human Mesenteric Artery and Vein. *J. Vasc. Res.* **2008**, *45*, 323–332. [CrossRef]
28. Khan, D.; Moffet, C.R.; Flatt, P.R.; Kelly, C. Role of islet peptides in beta cell regulation and type 2 diabetes therapy. *Peptides* **2018**, *100*, 212–218. [CrossRef]
29. Zhou, Q.; Melton, D.A. Pancreas regeneration. *Nature* **2018**, *557*, 351–358. [CrossRef]
30. Singh, M.; Webster, P.D. Neurohormonal control of pancreatic secretion. *Gastroenterology* **1978**, *74*, 294–309. [CrossRef]
31. Owyang, C.; Logsdon, C.D. New insights into neurohormonal regulation of pancreatic secretion. *Gastroenterology* **2004**, *127*, 957–969. [CrossRef] [PubMed]
32. Love, J.A.; Yi, E.; Smith, T.G. Autonomic pathways regulating pancreatic exocrine secretion. *Auton. Neurosci.* **2007**, *133*, 19–34. [CrossRef] [PubMed]
33. Konturek, S.J.; Konturek, J.; Lamers, C.B.; Tasler, J.; Bilski, J. Role of secretin and CCK in the stimulation of pancreatic secretion in conscious dogs. Effects of atropine and somatostatin. *Int. J. Pancreatol.* **1987**, *2*, 223–235. [CrossRef] [PubMed]
34. Phillips, M.E.; Hopper, A.D.; Leeds, J.S.; Roberts, K.J.; McGeeney, L.; Duggan, S.N.; Kumar, R. Consensus for the management of pancreatic exocrine insufficiency, UK practi-cal guidelines. *BMJ Open Gastroenterol.* **2021**, *8*, e000643. [CrossRef]

35. Keller, J.; Layer, P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* **2005**, *54*, vi1–vi28. [CrossRef]
36. Sachs, E.F.; Hurwitz, F.J.; Bloch, H.M.; Milne, F.J. Pancreatic exocrine hypofunction in the wasting syndrome of end-stage renal disease. *Am. J. Gastroenterol.* **1983**, *78*, 170–173.
37. Wang, S.; Ma, L.; Zhuang, Y.; Jiang, B.; Zhang, X. Screening and risk factors of exocrine pancreatic insufficiency in critically ill adult patients receiving enteral nutrition. *Crit. Care* **2013**, *17*, R171. [CrossRef]
38. Partelli, S.; Frulloni, L.; Minniti, C.; Bassi, C.; Barugola, G.; D'Onofrio, M.; Crippa, S.; Falconi, M. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. *Dig. Liver Dis.* **2012**, *44*, 945–951. [CrossRef]
39. Garcia, D.D.L.I.; Vallejo-Senra, N.; Iglesias-Garcia, J.; López-López, A.; Nieto, L.; Domínguez-Muñoz, J.E. Increased Risk of Mortality Associated with Pancreatic Exocrine Insufficiency in Patients with Chronic Pancreatitis. *J. Clin. Gastroenterol.* **2018**, *52*, e63–e72. [CrossRef]
40. Arvanitakis, M.; Ockenga, J.; Bezmarevic, M.; Gianotti, L.; Krznarić, Ž.; Lobo, D.N.; Löser, C.; Madl, C.; Meier, R.; Phillips, M.; et al. ESPEN guideline on clinical nutrition in acute and chronic pancreatitis. *Clin. Nutr.* **2020**, *39*, 612–631. [CrossRef]
41. Vanga, R.R.; Tansel, A.; Sidiq, S.; El-Serag, H.B.; Othman, M.O. Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-analysis. *Clin. Gastroenterol. Hepatol.* **2018**, *16*, 1220–1228.e4. [CrossRef] [PubMed]
42. Safdi, M.; Bekal, P.K.; Martin, S.; Saeed, Z.A.; Burton, F.; Toskes, P.P. The effects of oral pancreatic enzymes (Creon 10 cap-sule) on steatorrhea. A multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. *Pancreas* **2006**, *33*, 156–162. [CrossRef] [PubMed]
43. Whitcomb, D.C.; A Lehman, G.; Vasileva, G.; Malecka-Panas, E.; Gubergrits, N.; Shen, Y.; Sander-Struckmeier, S.; Caras, S. Pancrelipase Delayed-Release Capsules (CREON) for Exocrine Pancreatic Insufficiency due to Chronic Pancreatitis or Pancreatic Surgery: A Double-Blind Randomized Trial. *Am. J. Gastroenterol.* **2010**, *105*, 2276–2286. [CrossRef] [PubMed]
44. Bruno, M.J.; Haverkort, E.B.; Tijssen, G.P.; Tytgat, G.N.J.; van Leeuwen, D.J. Placebo controlled trial of enteric coated pan-creatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut* **1998**, *42*, 92–96. [CrossRef] [PubMed]
45. Panebianco, A.C.; Scott, S.M.; Dart, C.H.; Takaro, T.; Echegaray, H.M. Acute Pancreatitis following Extracorporeal Circulation. *Ann. Thorac. Surg.* **1970**, *9*, 562–568. [CrossRef]
46. Rose, D.M.; Ranson, J.H.C.; Cunningham, J.N.; Spencer, F.C. Patterns of Severe Pancreatic Injury Following Cardiopulmonary Bypass. *Ann. Surg.* **1984**, *199*, 168–172. [CrossRef]
47. Castillo, C.F.D.; Harringer, W.; Warshaw, A.L.; Vlahakes, G.J.; Koski, G.; Zaslavsky, A.M.; Rattner, D.W. Risk Factors for Pancreatic Cellular Injury after Cardiopulmonary Bypass. *N. Engl. J. Med.* **1991**, *8*, 382–387. [CrossRef]
48. Rattner, D.W.; Gu, Z.-Y.; Vlahakes, G.J.; Warshaw, A.L. Hyperamylasemia After Cardiac Surgery. Incidence, significance, and management. *Ann. Surg.* **1989**, *209*, 279–283. [CrossRef]
49. Nys, M.; Venneman, I.; Deby-Dupont, G.; Preiser, J.-C.; Vanbelle, S.; Albert, A.; Camus, G.; Damas, P.; Larbuisson, R.; Lamy, M. Pancreatic cellular injury after cardiac surgery with cardiopulmonary bypass. *Shock* **2007**, *27*, 474–481. [CrossRef]
50. Herline, A.J.; Pinson, C.W.; Wright, J.K.; Debelak, J.; Shyr, Y.; Harley, D.; Merrill, W.; Starkey, T.; Pierson, R.; Chapman, W.C. Acute pancreatitis after cardiac transplantation and other cardiac procedures: Case-control analysis in 24,631 patients. *Am. Surg.* **1999**, *65*, 819–825.
51. Haas, G.S.; Warshaw, A.L.; Daggett, W.M.; Aretz, H.T. Acute pancreatitis after cardiopulmonary bypass. *Am. J. Surg.* **1985**, *149*, 508–515. [CrossRef]
52. Dembiński, A.; Warzecha, Z.; Ceranowicz, P.; Stachura, J.; Tomaszewska, R.; Konturek, S.J.; Sendur, R.; Dembiński, M.; Pawlik, W.W. Pancreatic damage and regeneration in the course of ischemia-reperfusion induced pancreatitis in rats. *J. Physiol. Pharmacol.* **2001**, *52*, 221–235. [PubMed]
53. Vollmar, B.; Menger, M.D. Microcirculatory dysfunction in acute pancreatitis, A new concept of pathogenesis involving vasomotion-associated arteriolar constriction and dilation. *Pancreatology* **2003**, *3*, 181–190. [CrossRef] [PubMed]
54. Kusterer, K.; Enghofer, M.; Zendler, S.; Blochle, C.; Usadel, K.H. Microcirculatory changes in sodium taurocholate-induced pancreatitis in rats. *Am. J. Physiol. Liver Physiol.* **1991**, *260*, G346–G351. [CrossRef]
55. Yoshimura, A.; Ohmori, T.; Yamada, S.; Kawaguchi, T.; Kishimoto, M.; Iwanaga, T.; Miura, N.; Fukushima, R. Comparison of pancreatic and renal blood flow in a canine tachycardia-induced cardiomyopathy model. *J. Veter-Med. Sci.* **2020**, *82*, 836–845. [CrossRef]
56. Warshaw, A.L.; O'hara, P.J. Susceptibility of the Pancreas to Ischemic Injury in Shock. *Ann. Surg.* **1978**, *188*, 197–201. [CrossRef]
57. Reilly, P.M.; Toung, T.J.; Miyachi, M.; Schiller, H.J.; Bulkley, G.B. Hemodynamics of pancreatic ischemia in cardiogenic shock in pigs. *Gastroenterology* **1997**, *113*, 938–945. [CrossRef]
58. Yoshimura, A.; Ohmori, T.; Itou, K.; Ishi, R.; Matsumura, Y.; Wada, Y.; Kishimoto, M.; Iwanaga, T.; Miura, N.; Suzuki, K.; et al. Histopathological changes in the pancreas due to decreased pancreatic blood flow in a canine tachycardia-induced cardiomyopathy model. *J. Veter-Med. Sci.* **2021**, *83*, 780–783. [CrossRef]
59. Takahashi, T.; Yaginuma, N. Ischemic Injury of the Human Pancreas. Its Basic Patterns Correlated with the Pancreatic Microvasculature. *Pathol. Res. Pract.* **1985**, *179*, 645–651. [CrossRef]

60. Nagaya, N.; Uematsu, M.; Kojima, M.; Date, Y.; Nakazato, M.; Okumura, H.; Hosoda, H.; Shimizu, W.; Yamagishi, M.; Oya, H.; et al. Elevated Circulating Level of Ghrelin in Cachexia Associated with Chronic Heart Failure, Relationships between ghrelin and anabolic/catabolic factors. *Circulation* **2001**, *104*, 2034–2038. [CrossRef]
61. Schulze, P.C.; Kratzsch, J.; Linke, A.; Schoene, N.; Adams, V.; Gielen, S.; Erbs, S.; Moebius-Winkler, S.; Schuler, G. Elevated serum levels of leptin and soluble leptin receptor in patients with ad-vanced chronic heart failure. *Eur. J. Heart Fail.* **2003**, *5*, 33–40. [CrossRef]
62. Deis, T.; Balling, L.; Rossing, K.; Boesgaard, S.; Kistorp, C.M.; Wolsk, E.; Gøtze, J.P.; Rehfeld, J.F.; Gustafsson, F. Plasma Somatostatin in Advanced Heart Failure, Association with Cardiac Filling Pres-sures and Outcome. *Cardiology* **2020**, *145*, 769–778. [CrossRef] [PubMed]
63. Vujasinovic, M.; Tretjak, M.; Marolt, A.; Tepes, B.; Pusnik, C.S.; Kerbev, M.K. Is exocrine pancreatic insufficiency result of decreased splanchnic circulation in patients with chronic heart failure? *JOP* **2016**, *17*, 201–203. [CrossRef]
64. Özcan, M.; Öztürk, G.Z.; Köse, M.; Emet, S.; Aydın, Ş.; Arslan, K.; Arman, Y.; Akkaya, V.; Tükek, T. Evaluation of malnutrition with blood ghrelin and fecal elastase levels in acute de-compensated heart failure patients. *Turk. Kardiyol. Dern. Ars.* **2015**, *43*, 131–137.
65. Xia, T.; Chai, X.; Shen, J. Pancreatic exocrine insufficiency in patients with chronic heart failure and its possible association with appetite loss. *PLoS ONE* **2017**, *12*, e0187804. [CrossRef] [PubMed]
66. Comfort, M.; Gambill, E.; Baggenstoss, A. Chronic relapsing pancreatitis, a study of twenty-nine cases without associated disease of the biliary or gastro-intestinal tract. *Gastroenterology* **1946**, *6*, 376–408.
67. Takahashi, H.; Okamura, D.; Starr, M.E.; Saito, H.; Evers, B.M. Age-dependent reduction of the PI3K regulatory subunit p85α suppresses pancreatic acinar cell proliferation. *Aging Cell* **2011**, *11*, 305–314. [CrossRef]
68. Von Figura, G.; Wagner, M.; Nalapareddy, K.; Hartmann, D.; Kleger, A.; Guachalla, L.M.; Rolyan, H.; Adler, G.; Rudolph, K.L. Regeneration of the Exocrine Pancreas Is Delayed in Telomere-Dysfunctional Mice. *PLoS ONE* **2011**, *6*, e17122. [CrossRef]
69. Hayashi, K.; Takahashi, T.; Kakita, A.; Yamashina, S. Regional differences in the cellular proliferation activity of the regener-ating rat pancreas after partial pancreatectomy. *Arch. Histol. Cytol.* **1999**, *62*, 337–346. [CrossRef]
70. Elsasser, H.P.; Adler, G.; Kern, H.F. Time Course and Cellular Source of Pancreatic Regeneration Following Acute Pancreatitis in the Rat. *Pancreas* **1986**, *1*, 421–429. [CrossRef]
71. Löhr, J.; Panic, N.; Vujasinovic, M.; Verbeke, C. The ageing pancreas: A systematic review of the evidence and analysis of the consequences. *J. Intern. Med.* **2018**, *283*, 446–460. [CrossRef] [PubMed]
72. Wynne, H.A.; Cope, L.H.; Mutch, E.; Rawlins, M.D.; Woodhouse, K.W.; James, O.F.W. The effect of age upon liver volume and apparent liver blood flow in healthy man. *Hepatology* **1989**, *9*, 297–301. [CrossRef] [PubMed]
73. Tsushima, Y.; Kusano, S. Age-Dependent Decline in Parenchymal Perfusion in the Normal Human Pancreas, Measurement by dynamic computed tomography. *Pancreas* **1998**, *17*, 148–152. [CrossRef] [PubMed]
74. Herzig, K.-H.; Purhonen, A.-K.; Räsänen, K.M.; Idziak, J.; Juvonen, P.; Phillps, R.; Walkowiak, J. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC Geriatr.* **2011**, *11*, 4. [CrossRef]
75. Laugier, R.; Bernard, J.-P.; Berthezene, P.; Dupuy, P. Changes in Pancreatic Exocrine Secretion with Age: Pancreatic Exocrine Secretion Does Decrease in the Elderly. *Digestion* **1991**, *50*, 202–211. [CrossRef] [PubMed]
76. Tal, M.G. Type 2 diabetes, Microvascular ischemia of pancreatic islets? *Med. Hypothes.* **2009**, *73*, 357–358. [CrossRef] [PubMed]
77. Freiburghaus, A.U.; Redha, F.; Ammann, R.W. Does Acute Pancreatitis Progress to Chronic Pancreatitis? A Microvascular Pancreatitis Model in the Rat. *Pancreas* **1995**, *11*, 374–381. [CrossRef]
78. Hackert, T.; Hartwig, W.; Fritz, S.; Schneider, L.; Strobel, O.; Werner, J. Ischemic acute pancreatitis: Clinical features of 11 patients and review of the literature. *Am. J. Surg.* **2009**, *197*, 450–454. [CrossRef]
79. Gullo, L.; Cavicchi, L.; Tomassetti, P.; Spagnolo, C.; Freyrie, A.; D'Addato, M. Effects of ischemia on the human pancreas. *Gastroenterology* **1996**, *111*, 1033–1038. [CrossRef]
80. McNeill, J.; Wilcox, W.C.; Pang, C.C.Y. Vasopressin and angiotensin, reciprocal mechanisms controlling mesenteric conduct-ance. *Am. J. Physiol.* **1977**, *232*, H260–H266.
81. Bailey, R.W.; Bulkley, G.B.; Hamilton, S.R.; Morris, J.B.; Haglund, U.H.; Meilahn, J.E. The fundamental hemodynamic mech-anism underlying gastric "stress ulceration" in cardiogenic shock. *Ann. Surg.* **1987**, *205*, 597–612. [CrossRef] [PubMed]
82. Gunther, S.; A GimbroneJr, M.; Alexander, R.W. Identification and characterization of the high affinity vascular angiotensin II receptor in rat mesenteric artery. *Circ. Res.* **1980**, *47*, 278–286. [CrossRef] [PubMed]
83. Leung, P.S.; Chappell, M.C. A local pancreatic renin-angiotensin system: Endocrine and exocrine roles. *Int. J. Biochem. Cell Biol.* **2003**, *35*, 838–846. [CrossRef]
84. Sakurai, T.; Kudo, M.; Fukuta, N.; Nakatani, T.; Kimura, M.; Park, A.-M.; Munakata, H. Involvement of Angiotensin II and Reactive Oxygen Species in Pancreatic Fibrosis. *Pancreatology* **2011**, *11*, 7–13. [CrossRef]
85. Sherlock, S. The Liver in Heart Failure Relation of Anatomical, Functional, and Circulatory Changes. *Heart* **1951**, *13*, 273–293. [CrossRef]
86. Kuroda, T.; Hirooka, M.; Koizumi, M.; Ochi, H.; Hisano, Y.; Bando, K.; Matsuura, B.; Kumagi, T.; Hiasa, Y. Pancreatic congestion in liver cirrhosis correlates with impaired insulin secretion. *J. Gastroenterol.* **2014**, *50*, 683–693. [CrossRef]

87. Imamura, Y.; Kumagi, T.; Kuroda, T.; Koizumi, M.; Yoshida, O.; Kanemitsu, K.; Tada, F.; Tanaka, Y.; Hirooka, M.; Hiasa, Y. Pancreas stiffness in liver cirrhosis is an indicator of insulin secretion caused by portal hypertension and pancreatic congestion. *Hepatol. Res.* **2021**, *51*, 775–785. [CrossRef]
88. Bhanot, U.K.; Möller, P. Mechanisms of parenchymal injury and signaling pathways in ectatic ducts of chronic pancreatitis, Iimplications for pancreatic carcinogenesis. *Lab. Inv.* **2009**, *89*, 489–497. [CrossRef]
89. Braganza, J.M.; Lee, S.H.; McCloy, R.F.; McMahon, M.J. Chronic pancreatitis. *Lancet* **2011**, *377*, 1184–1197. [CrossRef]
90. Habtezion, A. Inflammation in acute and chronic pancreatitis. *Curr. Opin. Gastroenterol.* **2015**, *31*, 395–399. [CrossRef]
91. Whitcomb, D.C. Clinical practice. Acute pancreatitis. *N. Engl. J. Med.* **2006**, *354*, 2142–2150. [CrossRef] [PubMed]
92. Sah, R.P.; Garg, P.; Saluja, A.K. Pathogenic mechanisms of acute pancreatitis. *Curr. Opin. Gastroenterol.* **2012**, *28*, 507–515. [CrossRef] [PubMed]
93. Gukovskaya, A.S.; Gukovsky, I.; Zaninovic, V.; Song, M.; Sandoval, D.; Pandol, S.J. Pancreatic acinar cells produce, release, and respond to tumor necrosis factor-alpha. Role in regulating cell death and pancreatitis. *J. Clin. Investig.* **1997**, *100*, 1853–1862. [CrossRef] [PubMed]
94. Hoque, R.; Farooq, A.; Mehal, W.Z. Sterile inflammation in the liver and pancreas. *J. Gastroenterol. Hepatol.* **2013**, *28*, 61–67. [CrossRef]
95. Goecke, H.; Forssmann, U.; Uguccioni, M.; Friess, H.; Conejo-Garcia, J.R.; Zimmermann, A.; Baggiolini, M.; Büchler, M.W. Macrophages infiltrating the tissue in chronic pancreatitis express the chem-okine receptor CCR5. *Surgery* **2000**, *128*, 806–814. [CrossRef]
96. Emmrich, J.; Weber, I.; Nausch, M.; Sparmann, G.; Koch, K.; Seyfarth, M.; Löhr, M.; Liebe, S. Immunohistochemical Characterization of the Pancreatic Cellular Infiltrate in Normal Pancreas, Chronic Pancreatitis and Pancreatic Carcinoma. *Digestion* **1998**, *59*, 192–198. [CrossRef]
97. Niederau, C.; Niederau, M.; Lüthen, R.; Strohmeyer, G.; Ferrell, L.D.; Grendell, J.H. Pancreatic exocrine secretion in acute experimental pancreatitis. *Gastroenterology* **1990**, *99*, 1120–1127. [CrossRef]
98. Evander, A.; Hederström, E.; Hultberg, B.; Ihse, I. Exocrine Pancreatic Secretion in Acute Experimental Pancreatitis. *Digestion* **1982**, *24*, 159–167. [CrossRef]
99. Vincent, D.; Myriam, D.; Frederic, C.; Jacques, D.; Dumasy, V.; Delhaye, M.; Cotton, F.; Deviere, J. Fat Malabsorption Screening in Chronic Pancreatitis. *Am. J. Gastroenterol.* **2004**, *99*, 1350–1354. [CrossRef]
100. Boreham, B.; Ammori, B. A prospective evaluation of pancreatic exocrine function in patients with acute pancreatitis: Correlation with extent of necrosis and pancreatic endocrine insufficiency. *Pancreatology* **2003**, *3*, 303–308. [CrossRef]
101. Hollemans, R.A.; Hallensleben, N.D.; Mager, D.J.; Kelder, J.C.; Besselink, M.G.; Bruno, M.J.; Verdonk, R.C.; van Santvoort, H.C. Pancreatic exocrine insufficiency following acute pancreatitis: Systematic review and study level meta-analysis. *Pancreatology* **2018**, *18*, 253–262. [CrossRef] [PubMed]
102. Aukrust, P.; Gullestad, L.; Ueland, T.; Damås, J.K.; Yndestad, A. Inflammatory and anti-inflammatory cytokines in chronic heart failure, Potential therapeutic implications. *Ann. Med.* **2005**, *37*, 74–85. [CrossRef] [PubMed]
103. Levine, B.; Kalman, J.; Mayer, L.; Fillit, H.M.; Packer, M. Elevated Circulating Levels of Tumor Necrosis Factor in Severe Chronic Heart Failure. *N. Engl. J. Med.* **1990**, *323*, 236–241. [CrossRef] [PubMed]
104. Rauchhaus, M.; Doehner, W.; Francis, D.P.; Davos, C.; Kemp, M.; Liebenthal, C.; Niebauer, J.; Hooper, J.; Volk, H.-D.; Coats, A.S.; et al. Plasma Cytokine Parameters and Mortality in Patients with Chronic Heart Failure. *Circulation* **2000**, *102*, 3060–3067. [CrossRef] [PubMed]
105. Smit, M.D.; Maass, A.H.; de Jong, A.M.; Muller Kobold, A.C.; van Veldhuisen, D.J.; van Gelder, I.C. Role of inflammation in early atrial fibrillation recurrence. *Europace* **2012**, *14*, 810–817. [CrossRef]
106. Ukena, C.; Mahfoud, F.; Kindermann, M.; Kindermann, I.; Bals, R.; Voors, A.A.; van Veldhuisen, D.J.; Böhm, M. The cardiopulmonary continuum systemic inflammation as 'common soil' of heart and lung disease. *Int. J. Cardiol.* **2010**, *145*, 172–176. [CrossRef]
107. Markousis-Mavrogenis, G.; Tromp, J.; Ouwerkerk, W.; Devalaraja, M.; Anker, S.D.; Cleland, J.G.; Dickstein, K.; Filippatos, G.S.; van der Harst, P.; Lang, C.C.; et al. The clinical significance of interleukin-6 in heart failure, results from the BIOSTAT-CHF study. *Eur. J. Heart Fail.* **2019**, *21*, 965–973. [CrossRef]
108. Jahng, W.S.; Song, E.; Sweeney, G. Crosstalk between the heart and peripheral organs in heart failure. *Exp. Mol. Med.* **2016**, *48*, e217. [CrossRef]
109. Nijst, P.; Verbrugge, F.H.; Grieten, L.; Dupont, M.; Steels, P.; Tang, W.W.; Mullens, W. The Pathophysiological Role of Interstitial Sodium in Heart Failure. *J. Am. Coll. Cardiol.* **2015**, *65*, 378–388. [CrossRef]
110. Eckberg, D.L.; Drabinsky, M.; Braunwald, E. Defective Cardiac Parasympathetic Control in Patients with Heart Disease. *N. Engl. J. Med.* **1971**, *285*, 877–883. [CrossRef]
111. Brouwer, J.; Van Veldhuisen, D.J.; Man In't Veld, A.J.; Dunselman, P.H.; Boomsma, F.; Haaksma, J.; Lie, K.I.; Dutch Ibopamine Multicenter Trial (DIMT) Study Group. Heart rate variability in patients with mild to moderate heart failure, Effects of neurohormonal modulation by digoxin and ibopamine. *J. Am. Coll. Cardiol.* **1995**, *26*, 983–990. [CrossRef]
112. Tuininga, Y.; Van Veldhuisen, D.J.; Brouwer, J.; Haaksma, J.; Crijns, H.J.; Veld, A.J.M.I.; Lie, K.I. Heart rate variability in left ventricular dysfunction and heart failure: Effects and implications of drug treatment. *Heart* **1994**, *72*, 509–513. [CrossRef] [PubMed]

113. van den Berg, M.P.; Tjeerdsma, G.; Lefrandt, J.D.; Smit, A.J.; van den Meiracker, A.H.; van Roon, A.M.; Boomsma, F.; van Veldhuisen, D.J. Effect of lower body negative pressure in patients with mild conges-tive heart failure. *Am. J. Cardiol.* **2003**, *91*, 759–762. [CrossRef]
114. Newihi H el Dooley, C.P.; Saad, C.; Staples, J.; Zeidler, A.; Valenzuela, J.E. Impaired exocrine pancreatic function in diabetics with diarrhea and peripheral neuropathy. *Dig. Dis. Sci.* **1988**, *33*, 705–710. [CrossRef] [PubMed]
115. Sangnes, D.A.; Bergmann, E.S.; Moss, R.M.; Engjom, T.; Søfteland, E. Pancreatic exocrine insufficiency in diabetes is associated with autonomic dysfunction. *Scand. J. Gastroenterol.* **2021**, *56*, 1222–1228. [CrossRef]
116. Von Haehling, S.; Doehner, W.; Anker, S.D. Nutrition, metabolism, and the complex pathophysiology of cachexia in chronic heart failure. *Cardiovasc. Res.* **2007**, *73*, 298–309. [CrossRef]
117. Molfino, A.; Papa, A.; Gasperini-Zacco, M.L.; Muscaritoli, M.; Amoroso, A.; Cascino, A.; Catalano, C.; Albanese, C.V.; Laviano, A. Left ventricular mass correlates with lean body mass in patients with disease-associated wasting. *J. Cachexia Sarcopenia Muscle* **2014**, *5*, 251–252. [CrossRef]
118. Berry, C.; Clark, A.L. Catabolism in chronic heart failure. *Eur. Heart J.* **2000**, *21*, 521–532. [CrossRef]
119. Drott, C.; Persson, H.; Lundholm, K. Cardiovascular and metabolic response to adrenaline infusion in weight-losing patients with and without cancer. *Clin. Physiol.* **1989**, *9*, 427–439. [CrossRef]
120. Streng, K.W.; Hillege, H.L.; ter Maaten, J.M.; van Veldhuisen, D.J.; Dickstein, K.; Ng, L.L.; Samani, N.J.; Metra, M.; Ponikowski, P.; Cleland, J.G.; et al. Clinical implications of low estimated protein intake in patients with heart failure. *J. Cachexia Sarcopenia Muscle* **2022**, *13*, 1762–1770. [CrossRef]
121. de Rijk, F.E.; van Veldhuisen, C.L.; Besselink, M.G.; van Hooft, J.E.; van Santvoort, H.C.; van Geenen, E.J.; Hegyi, P.; Löhr, J.-M.; Dominguez-Munoz, J.E.; de Jonge, P.J.F.; et al. Diagnosis and treatment of exocrine pancreatic insufficiency in chronic pancreatitis: An international expert survey and case vignette study. *Pancreatology* **2022**, *22*, 457–465. [CrossRef] [PubMed]
122. Bomer, N.; Pavez-Giani, M.G.; Beverborg, N.G.; Cleland, J.G.F.; van Veldhuisen, D.J.; van der Meer, P. Micronutrient deficiencies in heart failure: Mitochondrial dysfunction as a common pathophysiological mechanism? *J. Intern. Med.* **2022**, *291*, 713–731. [CrossRef] [PubMed]
123. Schöttker, B.; Haug, U.; Schomburg, L.; Köhrle, J.; Perna, L.; Müller, H.; Holleczek, B.; Brenner, H. Strong associations of 25-hydroxyvitamin D concentrations with all-cause, cardiovascular, cancer, and respiratory disease mortality in a large cohort study. *Am. J. Clin. Nutr.* **2013**, *97*, 782–793. [CrossRef]
124. Perna, L.; Schöttker, B.; Holleczek, B.; Brenner, H. Serum 25-Hydroxyvitamin D and Incidence of Fatal and Nonfatal Cardiovascular Events, A Prospective Study with Repeated Measurements. *J. Clin. Endocrinol. Metab.* **2013**, *98*, 4908–4915. [CrossRef]
125. Meems, L.M.; Van Der Harst, P.; Van Gilst, W.H.; De Boer, R.A. Vitamin D biology in heart failure: Molecular mechanisms and systematic review. *Curr. Drug Targets* **2011**, *12*, 29–41. [CrossRef] [PubMed]
126. Meems, L.M.G.; De Borst, M.H.; Postma, D.S.; Vonk, J.M.; Kremer, H.P.H.; Schuttelaar, M.-L.A.; Rosmalen, J.; Weersma, R.K.; Wolffenbuttel, B.H.R.; Scholtens, S.; et al. Low levels of vitamin D are associated with multimorbidity: Results from the LifeLines Cohort Study. *Ann. Med.* **2015**, *47*, 474–481. [CrossRef]
127. Liu, L.C.; Voors, A.A.; Van Veldhuisen, D.J.; van der Veer, E.; Belonje, A.M.; Szymanski, M.K.; Silljé, H.H.; van Gilst, W.; Jaarsma, T.; De Boer, R.A. Vitamin D status and outcomes in heart failure patients. *Eur. J. Heart Fail.* **2011**, *13*, 619–625. [CrossRef]
128. Schroten, N.F.; Ruifrok, W.P.; Kleijn, L.; Dokter, M.M.; Silljé, H.H.; Heerspink, H.J.L.; Bakker, S.J.; Kema, I.P.; van Gilst, W.H.; van Veldhuisen, D.J.; et al. Short-term vitamin D3 supplementation lowers plasma renin activity in pa-tients with stable chronic heart failure, an open-label, blinded end point, randomized prospective trial (VitD-CHF trial). *Am. Heart J.* **2013**, *166*, 357–364.e2. [CrossRef]
129. Zittermann, A.; Ernst, J.B.; Prokop, S.; Fuchs, U.; Dreier, J.; Kuhn, J.; Knabbe, C.; Birschmann, I.; Schulz, U.; Berthold, H.K.; et al. Effect of Vitamin D on all-causemortality in heart failure (EVITA), A 3-year ran-domized clinical trial with 4000 IU Vitamin D daily. *Eur. Heart J.* **2017**, *38*, 2279–2286. [CrossRef]
130. de Boer, R.A.; Meems, L.M.G.; van Veldhuisen, D.J. Vitamin D supplementation in heart failure, Case closed? *Eur. Heart J.* **2017**, *38*, 2287–2289. [CrossRef]
131. Zittermann, A.; Ernst, J.B.; Prokop, S.; Fuchs, U.; Dreier, J.; Kuhn, J.; Berthold, H.K.; Pilz, S.; Gouni-Berthold, I.; Gummert, J.F. Vitamin D supplementation and bone turnover in advanced heart failure: The EVITA trial. *Osteoporos. Int.* **2017**, *29*, 579–586. [CrossRef] [PubMed]