European Radiology
https://doi.org/10.1007/s00330-017-5227-8

MAGNETIC RESONANCE

# Dynamic non-invasive ASL perfusion imaging of a normal pancreas with secretin augmented MR imaging

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Received: 18 July 2017 / Revised: 23 November 2017 / Accepted: 30 November 2017


## Abstract

**Objectives** To investigate prospectively the repeatability of pancreatic perfusion measurements using arterial spin labelling (ASL) and to determine the increase in perfusion due to secretin stimulation.

**Material and methods** An (FAIR)-TrueFISP ASL sequence was applied to determine the perfusion of the pancreatic head in a 3T MRI scanner. Ten healthy volunteers (four men, six women: mean age 28.5 ± 4.6 years; age range 25–40 years) were investigated twice within 1 week. The inter-individual variability was calculated using the standard deviation. Intra-individual agreement between the first and second scan was estimated using the Pearson correlation coefficient. A paired Wilcoxon rank-sum test was used to compare perfusion at baseline (BL) and during secretin stimulation.

**Results** The mean BL perfusion of the pancreatic head was 285 ± 96 mL/100 g/min with an intra-individual correlation coefficient of 0.67 (strong) for repeated measurements. Secretin stimulation led to a significant increase (by 81%) in perfusion of the pancreatic head to 486 ±156 mL/100 g/min ($p$=0.002) with an intra-individual correlation of 0.29 (weak). A return to BL values was observed after 239 ± 92 s with a moderate intra-individual correlation coefficient of 0.42 for repeat measurements.

**Conclusion** Dynamic non-invasive ASL imaging of the pancreas permitted quantification of pancreatic perfusion in a clinically applicable setting.

**Key Points**

- *ASL imaging of the pancreas permitted quantification of pancreatic perfusion*
- *Secretin stimulation led to a significant increase in pancreatic perfusion*
- *The intra-individual correlation coefficient for baseline perfusion was strong for repeated measurements*

**Keywords** Pancreas · MRI · Secretin · Perfusion · Arterial spin labelling

**Abbreviations**

| | |
|---|---|
| ASL | Arterial spin labelling |
| BL | Baseline |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| MDCT | Multi-detector computed tomography |
| FAIR | Flow-sensitive alternating inversion recovery |
| M0 | Tissue equilibrium magnetization |
| TI | Inversion time |
| TR | Repetition time |
| TE | Echo time |
| ROI | Region of interest |
| ΔM | Magnetization difference |

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## Introduction

Analysis of tissue perfusion represents a sensitive physiological marker for the diagnosis of pancreatic disease. The most common pathologies of the pancreas include inflammatory

Published online: 04 January 2018

processes and neoplastic diseases. The ability to distinguish between these two pathologies has significant therapeutic and prognostic implications. It has been shown that pancreatic blood flow is altered in patients with chronic pancreatitis, which leads to the idea that perfusion assessment can be used as an additional clinical parameter to differentiate pancreatic pathologies [1]. An initial attempt to characterize and differentiate pancreatic pathologies by assessing perfusion was reported by Delrue et al. [2]. This study reported a hypoperfusion of pancreatic tissue in both acute and chronic pancreatitis, which likely occurred due to the association between generalized oedema and consecutive release of pancreatic enzymes in acute pancreatitis. This association resulted in necrosis, destruction of small vessels and parenchymal haemorrhage [2]. Recently, Tian et al. published results, which showed a poorer perfusion in mild acute pancreatitis using MDCT perfusion measurements [3]. Ketwaroo et al. showed in a long-term follow-up study that the negative predictive value of secretin pancreatic function testing was 97% to rule out chronic pancreatitis [4] and the duct-penetrating sign in secretin-enhanced MRCP is known to be suggestive of malignancy [5]. However, whether perfusion imaging using ASL with secretin injection can distinguish malignant processes from inflammatory conditions is not investigated yet.

MRI has been established as a reliable method for the detection of pancreatic diseases. In addition to the standard diagnostic tools, e.g., endoscopic ultrasound and endoscopic retrograde cholangiopancreatography (ERCP), MRI can non-invasively provide both morphological tissue characterization and an assessment of pancreatic function [6–8]. In addition to MRI, other methods have been employed quantitatively to assess pancreatic perfusion that are either invasive (endoscopy and laparoscopy) or require radiation (computed tomography, CT). Several methods have been proposed to non-invasively quantify pancreatic perfusion [8–10]. Bali et al. published results regarding the effects of secretin on the pancreas measured with dynamic contrast-enhanced MRI, and their results showed increased perfusion after secretin administration [8]. Sofuni et al. analysed the vascularity of pancreatic carcinomas using contrast-enhanced ultrasound along with differences observed in histology [9]. Another research group published preliminary data that suggested pancreatic perfusion measured with multi-detector computed tomography (MDCT) and perfusion imaging could help assess the severity of acute pancreatitis [10]. However, these approaches and other previous reports of pancreatic tissue perfusion quantification are all based on administering contrast media [11, 12]. Moreover, CT and PET perfusion imaging require substantial radiation exposure. Because of the high numbers of patients with comorbidities, as well as severe renal insufficiency and the general desire to reduce unnecessary radiation exposure, a strong need exists for an alternative diagnostic tool.

In recent years, arterial spin labelling (ASL) has been introduced as a tool for quantitative assessment of tissue perfusion without the need for administering contrast media [6]. ASL has been used in previous studies to measure perfusion of the pancreas and several other organs [6, 13–16]. The lack of contrast media use is a major advantage of this method because it permits repeated measurements and allows researchers to analyse repeatability.

Stimulation of the exocrine pancreas can be induced pharmacologically through administration of exogenous secretin, which is used clinically in secretin-stimulated MR cholangiopancreatography to temporarily change the pancreatic blood flow [8, 17]. However, quantification of pancreatic blood flow is challenging due to the complex anatomical structures of the pancreas and its location. The pancreas receives its blood supply from a rich plexus of vessels with the main arterial supply originating from the splenic artery in addition to the superior and inferior pancreaticoduodenal arteries [7].

Schraml et al. used a flow-sensitive alternating inversion recovery (FAIR)-TrueFISP sequence to analyse pancreatic tissue perfusion and assess baseline (BL) values in 10 healthy volunteers [6]. However, they did not investigate the physiological repeatability of this perfusion assessment method in the pancreas. Cox et al. showed significant temporal changes in pancreatic perfusion and blood flow in the arteries supplying the pancreas in response to secretin stimulation [7]. These findings appear promising. However, physiological repeatability has yet to be assessed. In addition, the re-test reliability remains unknown for the effects of secretin on pancreatic perfusion.

Given these limitations, the aims of this study were to prospectively investigate the repeatability of perfusion measurements in pancreatic tissue using ASL and to quantify perfusion changes after secretin stimulation in healthy volunteers.

## Methods and materials

### Study participants and study design

The local ethics committee approved this study, and written informed consent was obtained from all participants.

Participants who fulfilled all the following inclusion criteria were enrolled in the study: absence of systemic or pancreatic disease, no gastrointestinal symptoms, negative urine pregnancy test at screening if the subjects were female and no devices or metallic implants.

Ten healthy volunteers (four men, six women: mean age 28.5 ± 4.6; 25-40 years) were investigated after overnight fasting for at least 6 h. To investigate the repeatability of pancreatic perfusion, the volunteers were examined twice with an interval of one week between measurements. The repeated

scan after one week was performed at the same time of day (early in the morning). The volunteers did not follow any dietary restrictions and were not instructed to cease physical activity. All individuals were placed in an MRI magnet using a phased-array surface coil for image acquisition in the supine position. To reduce motion artefacts, individual datasets were collected while the subjects held their breath during the acquisition time of 13.2 s for each data set.

## MRI protocol

All scans were performed using a 3T MRI system (Verio; Siemens Erlangen, Germany). Slices for ASL measurements were selected based on a series of anatomical T2 HASTE sequences, and perfusion imaging was performed with the slice position angled along the axis of the pancreatic head. Within the same slice, a T1-map and tissue equilibrium magnetization (M0) were acquired by measuring an image without inversion. BL and post-secretin series were collected using the same slice orientation. Perfusion assessment was performed with a FAIR-TrueFISP ASL sequence to determine pancreatic perfusion. The following sequence parameters were used and are identical to parameters published by Schraml et al. [6]: 5 mm slices; 360x360 $mm^2$ field of view; 128x128 matrix; TI/TR/TE of 1200/4.04/2.02 ms; and 70° flip angle. This method combined the FAIR pulsed ASL technique with a TrueFISP data acquisition strategy [6, 15]. FAIR-TrueFISP ASL is based on global and selective inversion experiments [15]. An inversion time (TI) of 1200 ms was chosen for this study. T1 is the longitudinal relaxation time of pancreatic tissue, which was set to 600 ms based on values published in the literature [6, 18]. Two inversion recovery images were acquired in an interleaved manner, one recorded after a non-slice-selective global inversion pulse and another with a slice-selective inversion pulse (Fig. 1). Therefore, each data set contains two measurements with an acquisition time of 13.2 s. The total examination time for perfusion imaging of the entire organ was 17 min 36 s.

Two radiologists, including a fellow specializing in body imaging with 10 years of experience (W.K.) and a junior faculty radiologist with 2.5 years of body imaging experience (K.S.), performed all measurements and reviewed the scans. The region of interest (ROI) was set with the aid of an anatomical T2 HASTE image along the outline of the pancreatic head as determined by the consensus of these two radiologists, and then the ROI was automatically propagated for all remaining ASL datasets (Fig. 2). The datasets were co-registered before propagation of the ROI. As much pancreatic tissue was included in the ROI as possible with careful exclusion of large surrounding vessels and ducts (Fig. 1). During one imaging session, 80 consecutive ASL datasets were measured for dynamic tracking of the secretin effects in each pancreas. During the acquisition, the ASL measurements were divided

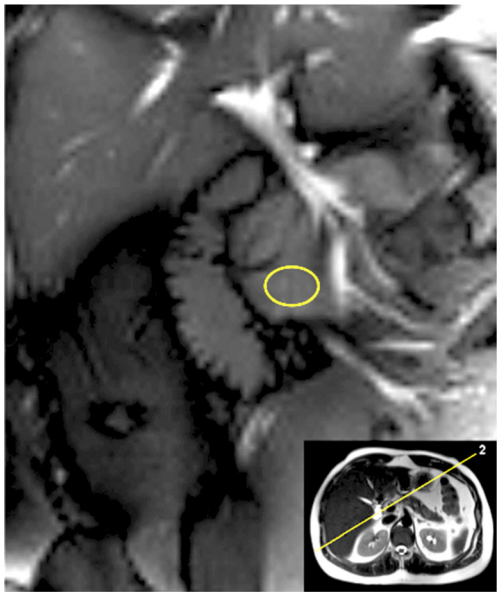


**Fig. 1** Slice-selective inversion image showing the pancreatic head and body in a 40-year-old volunteer holding his breath. The region of interest is shown in yellow

into four stacks. Each stack contained 20 datasets. The first of the resulting four stacks represented the BL value, whereas the following three stacks (P1-P3) were measured immediately after secretin injection (1 E/kg body weight) for dynamic tracking of the secretin effects in the pancreas (Fig. 2). The i.v. secretin injection was performed slowly over a period of 1 min. The first two datasets of each stack were excluded from analysis to reduce artefacts associated with irregular breathing. Therefore, each stack yielded 18 perfusion values. A sliding average was calculated for each stack, and the mean perfusion value was measured by averaging four perfusion values. In this manner; 15 sliding averages were calculated from each stack to provide a total of 60 mean perfusion values for the entire scan.

## Data analysis

Perfusion values were calculated from the analysis of the magnetization difference (ΔM) between slice-selective and global inversion images (Fig. 3). β is the blood-tissue water partition coefficient, which was assumed to have a constant value of 100 mL/100 g [19], and M0 is the undisturbed longitudinal magnetization [6]. TI represents the interval time between the inversion pulse and the central line of k-space acquisition in the TrueFISP sequence, as published in the literature [6].

Quantitative perfusion calculations were based on the extended Bloch equation using an in-house MatLab (MathWorks, Natick, MA, USA) program (Eq. 1).

$$Perfusion = \frac{\beta}{2T1}\frac{\Delta M}{M0}e^{\frac{TI}{T1}} \quad (1)$$

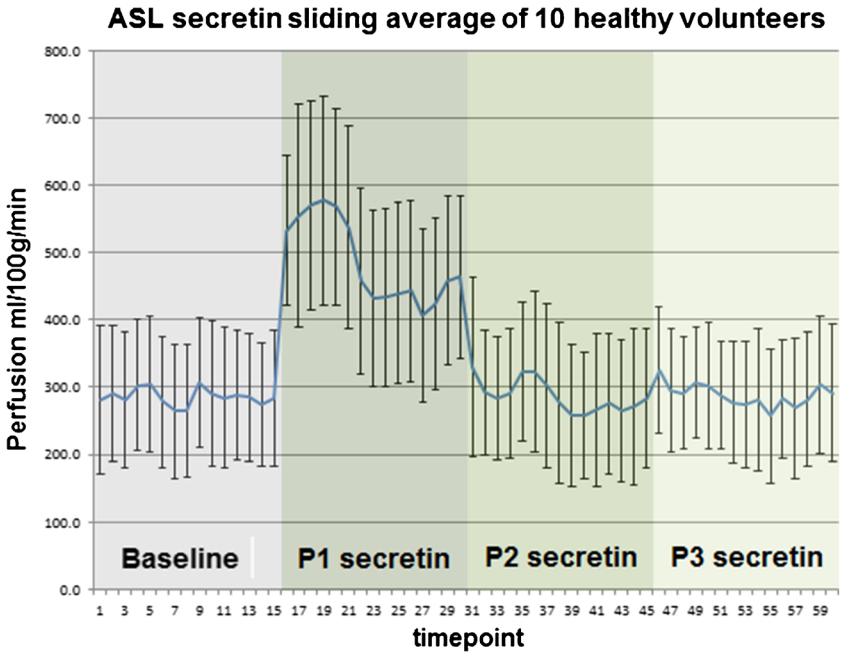


**Fig. 2** Mean ASL perfusion values of the pancreatic head for 10 volunteers with evaluation of temporal changes after secretin injection (P1). The mean baseline perfusion was 285 ± 96 mL/100 g/min. After secretin stimulation (P1), pancreatic perfusion was significantly ($p$<0.002) increased by 81% to 486 ± 156 mL/100 g/min. A return to baseline perfusion values was observed in the post-secretin stacks (P2, P3)

A perfusion map was calculated for each patient using equation (1) and the global and selective inversion images. Perfusion values were calculated and analysed using MatLab.

## Statistical analysis

A paired Wilcoxon rank-sum test was applied to compare perfusion before and during secretin stimulation. The statistical analysis was performed using MedCalc (MedCalc Software, Mariakerke, Ostend, Belgium), and $p$-values less than 0.05 were considered statistically significant. The inter-individual variability was estimated using the standard deviation. Intra-individual agreement between the first and second scans was assessed using the Pearson correlation coefficient.

## Results

Perfusion images showed a diagnostic image quality in the pancreatic head with limited motion artefacts. Precise delineation of the pancreas was feasible with the aid of anatomical axial T2 HASTE images. All healthy volunteers were free of

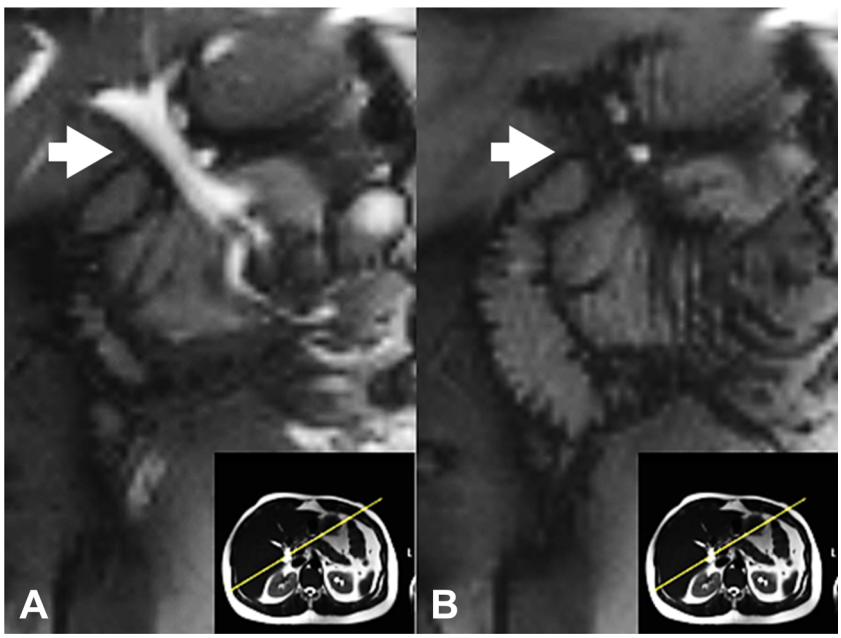


**Fig. 3** ASL perfusion imaging of a 40-year-old volunteer. Each dataset contained two measurements: one scan with a slice-selective inversion pulse (A) and one scan with a global inversion pulse (B). Arrowheads indicate the portal vein

visible pancreatic pathologies. No side effects were observed after secretin application. All 10 volunteers completed the study.

The mean BL perfusion was 285 ± 96 mL/100 g/min. The ASL perfusion values of the pancreatic head for all 10 volunteers are shown in Fig. 2. A strong intra-individual correlation coefficient of 0.67 (re-test reliability) was found between the BL pancreatic perfusion values obtained at the first MRI session and the second measurement after one week (Fig. 4). Pancreas perfusion was immediately significantly ($p$<0.002) increased by 81% to 486 ± 156 mL/100 g/min after secretin stimulation. This effect showed a weak intra-individual correlation coefficient of 0.29 for repeated pancreatic perfusion during secretin stimulation. A return to BL values was observed (P2 and P3, Fig. 2) at 239 ± 92 s after secretin stimulation with a moderate intra-individual correlation coefficient of 0.42 for repeated measurements (moderate re-rest reliability). After secretin stimulation, an indirect sign of the secretin effect was observed as the duodenum continuously filled with pancreatic fluid (Fig. 5).

## Discussion

Dynamic non-invasive ASL imaging of the pancreas permitted quantification of pancreas perfusion in a clinically applicable setting with good reproducibility for BL measurements. In addition, dynamic tracking of perfusion alterations was recorded after intravenous administration of secretin.

The BL perfusion values obtained in our study (285 ± 96 mL/100 g/min) are consistent with results from previous studies, which have reported mean values of 271 ± 79 mL/100 g/min [6] and 230 ± 87 mL/100 g/min [8] in the pancreatic head. Other researchers have obtained lower BL values (200 ± 25 mL/100 g/min) that are still within the error interval of our value [7], and slightly lower values of 184 ± 71 mL/100 g/min have been reported for the pancreatic head using contrast-enhanced MRI in healthy volunteers [8]. Comparing our BL values to the CT perfusion values by Miles et al. based on the "maximum slope model" we observe a discrepancy as they report BL perfusion values of 125-166 mL/100 mL/min. However, the BL values obtained in their study and others [20] are not comparable to our BL tissue perfusion values as they provide only relative perfusion values in relation to the aortic blood flow.

Because no reference standard exists for quantitative pancreatic perfusion measurements, the calculated BL perfusion values reported in our study and previous studies cannot be considered absolute values. The BL values obtained in this study served as reference values for determining the accuracy of our method. However, using an identical imaging protocol, our results showed similar perfusion values to the data published by Schraml et al. [6].

None of these previous studies using ASL perfusion of the pancreas investigated the reproducibility of ASL BL perfusion measurements in the pancreas [6, 7]. We report a strong intra-individual correlation coefficient of 0.67 (re-test reliability) for the BL perfusion value for repeated measurements without secretin stimulation with an interval of one week between measurements.

An exogenous secretin dose of 1 E/kg was administered to stimulate pancreatic tissue, which is known to result in the maximal response of the exocrine pancreas [21]. After secretin stimulation, healthy volunteers in this study showed a significant increase in pancreatic perfusion of 81% in the pancreatic head with reasonable reproducibility and peak perfusion values of 486 ± 156 mL/100 g/min with a re-test reliability of 0.29 (fair intra-individual correlation coefficient). Previous

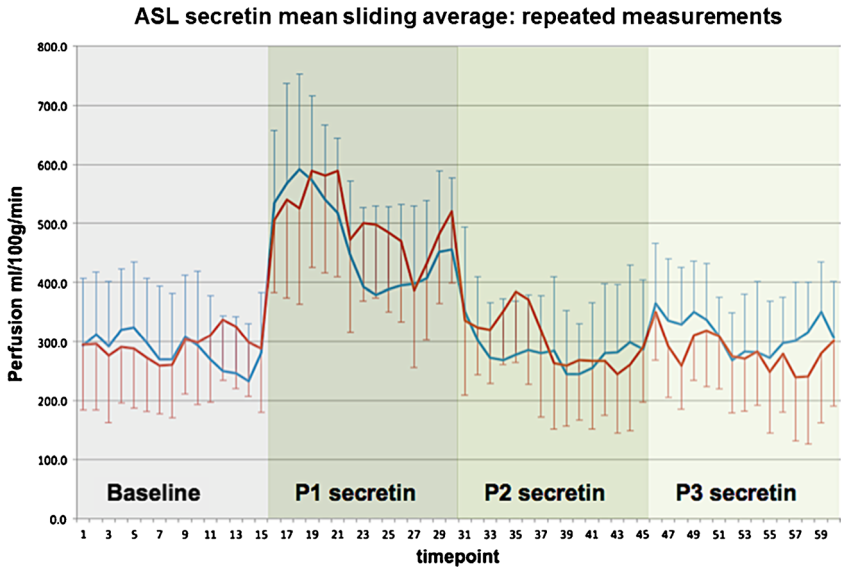


**Fig. 4** Mean ASL perfusion values of the pancreatic head for 10 volunteers with repeated measurements after 1 week. A strong intra-individual correlation coefficient of 0.67 (re-test reliability) was found between baseline pancreatic perfusion values obtained at the first MRI session (blue line) and the second measurements after one week (red line). In both imaging session a significant increase of the pancreatic perfusion is observed after secretin injection (P1) and a return to baseline value (P2, P3)

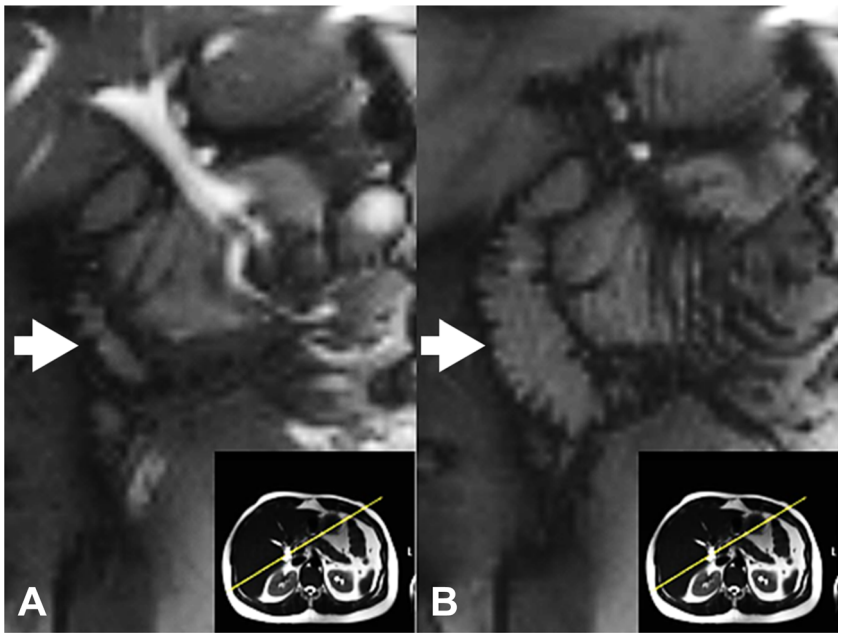


**Fig. 5** ASL perfusion imaging of a 40-year-old volunteer. The arrows indicate the duodenum before secretin stimulation (A) and filled with pancreatic fluid 4 min after secretin stimulation (B)

studies using secretin with other techniques, e.g., contrast-enhanced MRI or contrast-enhanced CT, have demonstrated that secretin application increases pancreatic perfusion [8, 10, 22]. Bali et al. used secretin augmented contrast-enhanced MRI and showed a significant increase in pancreatic perfusion within 1 min after secretin stimulation which is consistent with our results and showed an intra-individual variability of 21% for BL values [8]. However, their study was limited to a single time point, which precluded evaluation of temporal changes.

Fukukura et al. evaluated the pancreatic duct after administration of secretin with MR cholangiopancreatography and reported best visualization of the main pancreatic duct after 4.7 +/- 1.6 min, which supports our data [23].

Cox et al. measured the vessel flow using ASL and show that intravenous secretin administration resulted in a significant increase in pancreatic perfusion and arterial blood flow [7], which supports our results. They used a slower injection rate over a time course of 3 min than the 1-min time course used in the present study. They report a maximal increase at 5 min and increased pancreatic perfusion maintaining for 40 min. The return to BL values in our study was observed much earlier (239 ± 92 s after secretin injection), and peak perfusion values were seen immediately after secretin administration.

Further investigation is required to determine whether the time course has an impact on the secretin effect. In addition, a direct comparison of temporal changes in pancreatic perfusion after secretin administration assessed with ASL and contrast-enhanced MRI would be useful to examine in a future study.

The intra-individual correlation for repeated measurements was much higher before secretin stimulation than during the stimulation. A possible explanation for this discrepancy could be that the physiological response of the exocrine pancreas to secretin stimulation was influenced by factors that were not controlled. For example, volunteer physical activity prior to the examination may have affected the results, and this is one limitation of the current study. However, the secretin effects responsible for the 81% increase in perfusion in the pancreatic head showed higher amplitudes than the intra-individual variability for repeated measurements after secretin administration.

Another limitation of this study was the difference in physiology between our volunteer group and the typical patient. The patient population with pancreatic disease is considerably older than our volunteer group (mean age 28.5 ± 4.6; 25-40 years). Age-related changes in the pancreatic tissue (atrophy, lipomatosis and calcification) may result in changes of the MR signal characteristics, e.g., shortening of the pancreatic T1, and measurement of the individual T1 is recommended if this technique is to be used clinically [6].

Although all measurements were obtained while the subjects held their breath, through-plane motion artefacts cannot be avoided, which is a major limitation of using ASL on the abdomen. As a result, the $\Delta M$ could be overestimated, which could have led to artificially elevated perfusion values [6].

In addition, only a small portion of the pancreas was analysed for the perfusion measurements as the ROI for this study was set in the pancreatic head. Given that the pancreatic arterial supply arises from several sources, the variations between the first measurements versus the second measurement could be in part due to a slightly different section of the pancreas being sampled for each measurement. The ASL measurements can only be performed in one slice at a time, which is also a limitation of this study. Coverage of the whole pancreas for ASL measurements is almost not feasible. This remains the main

advantage of contrast agents, especially when secretin-induced hyperperfusion could be used to screen for small lesions that could be anywhere in the pancreas.

In a clinical setting, this study protocol could be combined with routinely performed diagnostic MRI, and an additional scan time of approximately 18 min would be required for measuring the secretin effect. Because the post-secretin stacks (P2, P3) showed normalization of perfusion values similar to BL, the scan time could be significantly shortened by measuring only the first two stacks (BL and P1 with a total scan time of approximately 9 min). Besides additional scan time in clinical routine, ASL will represent challenges to many departments as it needs implementation of the sequence, skilled technicians and patient's preparation (fasting for 6 h). Assessment of perfusion alteration may be helpful for differentiating pancreatic pathologies. Bali et al. reported that quantitative DCE-MR parameters were significantly correlated with fibrosis and microvascular density [24]. Heverhagen et al. (20) and other researchers [25, 26] published results of MR perfusion measurements in the context of following up pancreatic transplant patients to examine the possibility of early identification of graft dysfunction. A more recent publication by Huh et al. contained a perfusion analysis of pancreatic tumours using CAIPIRINHA-VIBE in a test-bolus DCE-MRI setting [27]. Other investigators have shown perfusion characteristics of isoattenuating insulinomas using contrast-enhanced CT [28]. Evaluations of the blood perfusion of pancreatic tumours on contrast-enhanced images were correlated with microvascular density and the histological changes of pancreatic carcinomas [29].

In summary, perfusion measurements with ASL sequences are a promising method e.g. for characterizing and monitoring therapy of pancreatic disorders without the risks associated with invasive alternatives. This method could be combined with routinely performed diagnostic MRI protocols to assess pancreatic tissue perfusion.

**Funding** The authors state that this work has not received any funding.

**Compliance with ethical standards**

**Guarantor** The scientific guarantor of this publication is Johannes Heverhagen.

**Conflict of interest** The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

**Statistics and biometry** One of the authors has significant statistical expertise.

**Informed consent** Written informed consent was obtained from all subjects (patients) in this study.

**Ethical approval** Institutional Review Board approval was obtained.

**Methodology**
- prospective
- observational
- performed at one institution

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