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CLINICAL INVESTIGATION IMAGING

Chemosaturation Percutaneous Hepatic Perfusion (CS-PHP) with Melphalan: Evaluation of 2D-Perfusion Angiography (2D-PA) for Leakage Detection of the Venous Double-Balloon Catheter

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Abstract

Purpose To evaluate the feasibility of 2D-perfusion angiography (2D-PA) for detecting leakage of the double-balloon catheter used for chemosaturation percutaneous hepatic perfusion (CS-PHP).

Materials and Methods Overall, 112 CS-PHP (09/2015-09/2018) in 52 patients were retrospectively screened for leakage alongside the double-balloon catheter on standard venograms. Finally, 18 procedures with visually detected leakage were included. Fifteen consecutive procedures without leakage served as control. To evaluate 2D-PA for leakage detection, the acquired digital subtraction venograms were post-processed. For each balloon, two different target ROIs were evaluated to assess a possible impact of localization and shape of the ROIs. Time to peak (TTP), peak density (PD), area under the curve (AUC), and ratios of target ROI/reference ROIs (PD_{tROI}/PD_{REF}; AUC_{tROI}/AUC_{REF}; and TTP_{tROI}/TTP_{REF}) were calculated.

Results Leakages were located as follows: 15/18 cranial and 3/18 caudal. At the cranial balloon both ROIs showed a significant decrease in PD_{tROI}/PD_{REF} and AUC_{tROI}/AUC_{REF} (ROI1: $p < 0.0001$; $p < 0.0001$; ROI2: $p < 0.0001$; $p < 0.0001$) and a significant increase in TTP_{tROI}/TTP_{REF} (ROI1: $p = 0.0009$; ROI2: $p = 0.0003$) after double-balloon correction. Following balloon adjustment, the 2D-PA ratios (PD and AUC) of the tested ROIs differed significantly ($p < 0.05$). The inter-individual comparison of the 2D-PA parameters of the group with leakage before balloon correction and the non-leakage group showed significantly different 2D-PA values for the

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cranial balloon in both ROIs ($p < 0.05$). No significant differences were found for the caudal balloon.
Conclusion 2D-PA provides a feasible tool for detecting leakages alongside the cranial portion of the double-balloon catheter used in CS-PHP. The shape and position of the ROIs used to assess perfusion and flow have an impact on the measurements.

Keywords 2D-perfusion angiography · Chemosaturation · Percutaneous hepatic perfusion · Double-balloon catheter · Leakage

Abbreviations

2D-PA	2D-perfusion angiography
ACT	Activated clotting time
AUC	Area under the curve
AUC_{tROI}/AUC_{REF}	Ratio of the target ROI to the reference ROI for AUC
CS-PHP	Chemosaturation percutaneous hepatic perfusion
DSA	Digital subtraction angiography
IVC	Inferior vena cava
PD	Peak density
PD_{tROI}/PD_{REF}	Ratio of the target ROI to the reference ROI for PD
ROI	Region of interest
REF	Reference region of interest
TACE	Transarterial chemoembolization
TIPS	Transjugular intrahepatic portosystemic shunt
tROI	Target region of interest
TTP	Time to peak
TTP_{tROI}/TTP_{REF}	Ratio of the target ROI to the reference ROI for TTP

Introduction

Chemosaturation percutaneous hepatic perfusion (CS-PHP) with melphalan is providing a novel, locoregional, therapeutic concept for unresectable primary malignancies or unresectable hepatic metastases [1–3].

In CS-PHP, high doses of melphalan are delivered directly to the liver through a catheter positioned in the hepatic arteries [3]. In order to avoid systemic toxicity, a double-balloon catheter is used to isolate the hepatic segment of the inferior vena cava (IVC). A pump extracts the venous blood from the liver which is then filtered through an extracorporeal melphalan-specific filtration system and returned through a sheath in the right jugular vein [3]. For proper isolation of the hepatic venous blood, the cranial balloon of the double-balloon catheter is placed in the right atrium, inflated, and then pulled back into the cavoatrial junction in order to prevent blood flow into the right atrium [3, 4]. The caudal balloon is then inflated in the IVC distal to the liver veins in order to prevent distal leakage of the melphalan-enriched blood [2]. The efficiency of the used filtration system is reported to be 86–93% [5–7].

Precise monitoring of the balloon position and inflation is essential in order to avoid leakages alongside the balloons which could expose the patients to highly toxic doses of melphalan. Typically, digital subtraction venograms acquired through a separate port of the catheter in breath-hold combined with a short interruption of the extracorporeal circuit are used to assess balloon positions, possible leakages, and retrograde opacification of the hepatic veins. To date, leakage detection depends on visual assessment which, however, is highly subjective and operator dependent. Furthermore, the experience of the interventional radiologist performing this relatively new technique is of major importance.

Recent studies described 2D-perfusion angiography (2D-PA) as a technique used to measure and quantify blood flow and tissue perfusion based on designated post-processing of standard DSA images [8–14]. Therefore, 2D-PA has the potential to detect blood flow alongside the double-balloon catheter and may offer a more objective assessment of leakage in the setting of CS-PHP.

The purpose of this study is to evaluate the feasibility of 2D-PA as a tool for detecting leakages of the double-balloon catheter used in CS-PHP in order to improve the safety of the procedure.

Material and Methods

Patient Selection

The local ethics committee approved this retrospective study. All patients were evaluated by an interdisciplinary tumor board. Between 09/2015 and 09/2018, 52 patients with unresectable liver tumors were scheduled for CS-PHP treatment and underwent 112 consecutive CS-PHPs. All interventions were retrospectively reviewed for possible leakage alongside the double-balloon catheter. Finally, 18/112 procedures in 12 patients with leakage [cranial $n = 15$; caudal ($n = 3$)] and consecutive balloon adjustment were included in the study. In addition, 15 consecutive procedures without visually detectable leakages were used as control.

Chemosaturation

The procedures were performed in an interventional radiology suite with the patient under general anesthesia [1, 7, 15]. A dedicated CS-PHP system (CHEMOSAT® second generation, Delcath Systems Inc., New York, NY, USA) was used, as previously described [2]. A microcatheter was advanced to the hepatic arteries and used for arterial chemoperfusion of the liver with a dosage of 3.0 mg/kg per ideal body weight up to a maximum dose of 220 mg of melphalan [2]. The double-balloon catheter was then inserted through a femoral vein and facilitated isolation of the hepatic vena cava segment after balloon inflation. A digital subtraction venogram of the excluded vena cava segment under transient respiratory- and pump-arrest was used to check the balloon position and to exclude leakages. The venogram was acquired by hand injection of 15 cc of contrast media through a dedicated side port of the double-balloon catheter. If necessary, the double-balloon was deflated, repositioned, and inflated and the venogram was repeated. The melphalan solution was administered, as previously described [2].

Image Analysis

The post-processing of the acquired venogram was performed on a dedicated workstation (syngo X Workplace® VD10A, Siemens Healthcare). In consensus, two radiologists (J.B.H. and C.L.A.D.) agreed upon the ROI placement. Leakage detection was carried out using different ROIs, i.e., one reference ROI in the IVC between the balloons to assess contrast inflow and two differently shaped target ROIs placed at the cranial (ROI1 and ROI2) and/or caudal (ROI3 and ROI4) balloon (Fig. 1). The shape and position were held constant for the measurements before and after balloon adjustments. The respective reference ROI was fitted to cover at least the central two-thirds of the IVC diameter and was placed precisely in the middle between the balloons of the double-balloon catheter.

The target ROIs were of comparable size. ROI1 was shaped semicircular and was placed cap-like on top of the cranial balloon in the right atrium. ROI2 (cranial) and ROI3 (caudal) had an oval shape and were positioned along the equator of the balloon in order to measure leakage at its origin. ROI4 was shaped semicircular in the IVC directly adjacent to the caudal balloon. An example of ROI placement and the two different target ROIs for the cranial and caudal balloons are shown in Fig. 1.

The ROIs drawn on the pre-DSA images were semi-automatically copied to the corresponding post-DSA images. Numeric density values for time to peak (TTP), peak density (PD) value, and area under the time density curve (AUC) were acquired. Values are interpreted as previously described [11, 16].

The ratios of the reference ROI to target ROI pre- and post-adjustment of the balloon position were calculated for the cranial and caudal balloons (TTP_{tROI1}/TTP_{REF}; PD_{tROI1}/PD_{REF}; AUC_{tROI1}/AUC_{REF}; TTP_{tROI2}/TTP_{REF}; PD_{tROI2}/PD_{REF}; and AUC_{tROI2}/AUC_{REF}) and compared. To further assess correct leakage detection using 2D-PA at the cranial balloon, the 2D-PA ratios of the leakages before balloon adjustment were compared to 15 additional CS-PHP procedures without leakage analyzed by 2D-PA using the same methodology. All of the images of the included patients underwent the same 2D-PA analysis.

Statistical Analysis

Descriptive statistical analyses of the patient demographics and angiographic data were computed. The values are presented as the mean values with standard deviation. Differences in 2D-PA values and two tested ROIs at both balloons before and after adjustment were compared using a pairwise Wilcoxon signed-rank test. Differences between the leakage group and the control group were tested using the Mann–Whitney U test. A p value of < 0.05 was defined as statistically significant. Statistical analyses were performed using commercially available software (JMP 12, SAS Institute, JMP Office Germany, Böblingen, Germany).

Results

Overall, 18 procedures performed in 12 patients (two men and 10 women; age 58 ± 8 years) with leakages were included. The leakages were located as follows: 15/18 at the cranial balloon at the cavoatrial junction and 3/18 at the caudal balloon at the renal/infrarenal IVC segment. Detailed patients' demographics as well as the clinical and interventional parameters are presented in Table 1.

2D-PA facilitated detection of leakages in all 18 procedures. After adjustment of the cranial balloon, both ROIs showed a significant decrease in PD_{tROI}/PD_{REF} (ROI1: − 80%, $p = < 0.0001$; ROI2: − 61%, $p = < 0.0001$) and AUC_{tROI}/AUC_{REF} (ROI1: − 83%, $p = < 0.0001$; ROI2: − 53%, $p = < 0.0001$) and a significant increase in TTP_{tROI}/TTP_{REF} (ROI1: + 32%, $p = 0.0009$; ROI2: + 55%, $p = 0.0003$). No significant changes in the 2D-PA parameters following balloon correction were found at the caudal balloon (all $p = 0.25$). Detailed results are displayed in Table 2. An example of 2D-PA leakage detection is shown in Fig. 2.

The 2D-PA values PD_{tROI}/PD_{REF} before balloon adjustment were significantly different to the control group without leakage for both ROIs (ROI1: $p < 0.0088$; ROI2:

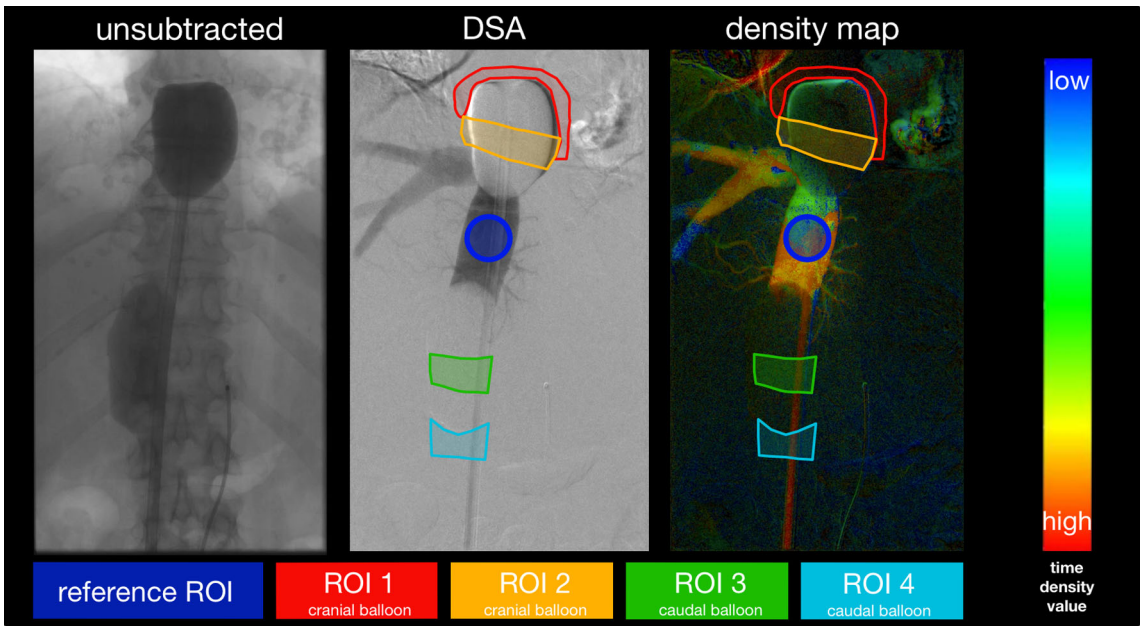

Fig. 1 Example of ROI placement. Images of a 75-year-old female patient with hepatic metastasis from uveal melanoma and who underwent CS-PHP. The reference ROI (blue) is positioned in the inferior vena cava between both balloons of the double-balloon catheter. The target ROIs are placed at the top of the cranial (ROI1—red) or caudal (ROI4—light blue) balloons and at the equator of the balloons (cranial ROI2—yellow; caudal ROI3—green). The time density value is color-coded

$p < 0.0005$) and AUC_{tROI}/AUC_{REF} (ROI1: $p < 0.0067$; ROI2: $p < 0.0022$). No difference was detected for TTP_{tROI}/TTP_{REF} (ROI1: $p = 0.95$; ROI2: $p = 0.85$).

When comparing ROI1 and ROI2 before balloon adjustment, PD_{tROI}/PD_{REF} of ROI1 was slightly higher compared to ROI2 ($p = 0.05$). After adjustment of the cranial balloon, the 2D-PA parameter ratios of the two tested ROIs were significantly different, i.e., PD_{tROI}/PD_{REF} ($p = 0.0353$), TTP_{tROI}/TTP_{REF} ($p = 0.0078$), and AUC_{tROI}/AUC_{REF} ($p = 0.0016$). In concordance with our findings for both ROIs after balloon adjustment PD_{tROI}/PD_{REF} ($p = < 0.0001$) and AUC_{tROI}/AUC_{REF} ($p = < 0.0001$) showed a significant difference at the cranial balloon when analyzing the non-leakage control group.

At the caudal balloon, no 2D-PA value showed a significant difference either following balloon correction or

Table 1 Patient demographics and clinical and interventional parameters

Parameters	Values
Location of leakage	15 cranial (83%); 3 caudal (17%)
Gender	10 females (83%); 2 males (17%)
Age (years)	58 ± 8
BMI	24 ± 5
ECOG	1 ± 1
ASA score	3 ± 1
Filling volume of cranial balloon (ml)	34 ± 6
Filling volume of caudal balloon (ml)	25 ± 6
Procedure time (min)	180 ± 26
Melphalan dose (mg)	145 ± 13
Underlying tumor entity	UM 7(58%); CC 3(25%); NET 1(8%); GB 1(8%)
Relevant previous surgery	
Hemihepatectomy	2 (17%)
Atypical segmental resection	3 (25%)

Shown are the mean values and SD

UM uveal melanoma, *CC* cholangiocarcinoma, *NET* neuroendocrine tumor, *GB* carcinoma of the gallbladder

Table 2 Changes of 2D-perfusion angiography parameters following balloon correction for all ROIs

	Pre-correction	Post-correction	Difference (%)	*p* value
Cranial balloon (n = 15)				
ROI1				
PD_{tROI1}/PD_{REF}	1.23 ± 0.8	0.24 ± 0.2	− 1 (− 80%)	< 0.0001
TTP_{tROI1}/TTP_{REF}	3.56 ± 1.4	4.7 ± 1.6	1.14 (32%)	0.0009
AUC_{tROI1}/AUC_{REF}	1.02 ± 0.6	0.17 ± 0.1	− 0.85 (− 83%)	< 0.0001
ROI2				
PD_{tROI2}/PD_{REF}	0.94 ± 0.5	0.37 ± 0.2	− 0.57 (− 61%)	< 0.0001
TTP_{tROI2}/TTP_{REF}	3.7 ± 1.3	5.74 ± 1.6	2.05 (55%)	0.0003
AUC_{tROI2}/AUC_{REF}	0.85 ± 0.5	0.32 ± 0.2	− 0.53 (− 62%)	< 0.0001
Caudal balloon (n = 3)				
ROI1				
PD_{tROI1}/PD_{REF}	0.32 ± 0.1	0.1 ± 0	− 0.22 (− 69%)	0.25
TTP_{tROI1}/TTP_{REF}	6.4 ± 1.9	4.44 ± 2	− 1.96 (− 31%)	0.25
AUC_{tROI1}/AUC_{REF}	0.25 ± 0.1	0.11 ± 0	− 0.14 (− 56)	0.25
ROI2				
PD_{tROI2}/PD_{REF}	0.24 ± 0.1	0.13 ± 0	− 0.11 (− 46%)	0.25
TTP_{tROI2}/TTP_{REF}	6.08 ± 1.8	3.1 ± 1.4	− 2.98 (− 49%)	0.25
AUC_{tROI2}/AUC_{REF}	0.22 ± 0.1	0.14 ± 0	− 0.08 (− 36)	0.25

Mean values and % difference between pre- and post-balloon correction

TTP time to peak, *PD* peak density, *AUC* area under the curve, *tROI* target region of interest, *REF* reference region of interest, PD_{tROI}/PD_{REF} ratio of the target ROI to the reference ROI for PD, AUC_{tROI}/AUC_{REF} ratio of the target ROI to the reference ROI for AUC, TTP_{tROI}/TTP_{REF} ratio of the target ROI to the reference ROI for TTP

when comparing the ROIs with the control group ($p > 0.05$). The 2D-PA parameters of the control group are summarized in Table 3.

Discussion

CS-PHP is currently performed in highly specialized centers in patients with liver metastasis with encouraging results [2, 3]. As the procedure will be disseminated in the IR community, improvements of the workflow might help to increase the acceptance and safety. Our study shows that 2D-PA is feasible and has the potential to help detect leakages alongside the balloons of the double-balloon catheter needed for CS-PHP. Furthermore, this study indicates that leakages are more common at the cranial balloon at the cavoatrial junction. The 2D-PA ratios, i.e., PD_{tROI}/PD_{REF}, AUC_{tROI}/AUC_{REF}, and TTP_{tROI}/TTP_{REF} measured at the cranial balloon for both ROIs, showed a significant change after adjustment of the balloon. Likewise, the PD_{tROI}/PD_{REF} and AUC_{tROI}/AUC_{REF} of the caudal balloons changed after adjustment without reaching statistical significance mainly due to the low overall number of leakages at the caudal balloon.

The aim of CS-PHP as regional therapy is to concentrate the chemotherapeutic effect on the targeted tumor tissue and to simultaneously avoid systemic toxicity. The high efficiency of the filtration system has been reported in several studies with a filtration rate between 86 and 93% [5–7]. Nevertheless, adverse events, especially concerning hematologic and cardiovascular toxicity, due to systemic melphalan exposure are frequently reported [1, 3, 17]. This can be caused by incomplete melphalan filtration, melphalan retention in healthy liver, liver tumors, and leakages alongside the double-balloon catheter. The latter can be prevented by optimizing the balloon position at the beginning of the procedure and by maintaining the position throughout the procedure. Review of the venograms to detect leakages is user dependent and requires experience with CS-PHP. Therefore, 2D-PA measurements offer a less subjective approach to easily detect contrast leakage alongside the balloons and thus might be useful to lower the systemic side effects of melphalan.

In 18 of 112 CS-PHPs a leakage was present with the majority detected at the cranial balloon (15/18; 83%). Anatomy at the balloon sites is fundamentally different. The funnel-shaped 3D geometry at the cavoatrial junction is more complex compared to the cylindrical shape of the infrahepatic inferior vena cava segment. Furthermore, movement of the heart not only adds to the complexity of the anatomic situation but also serves as pressure/suction pump and thus might actively suck blood into the atrium.

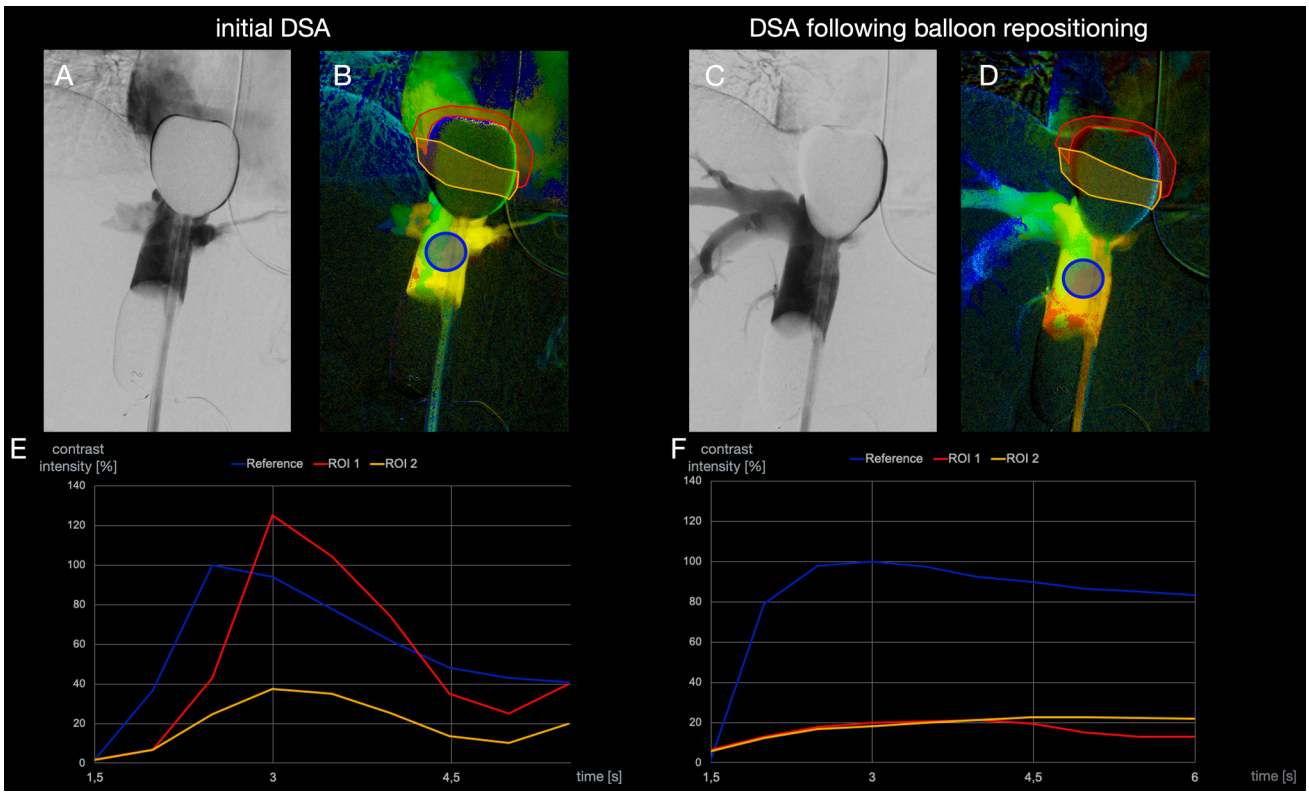

Fig. 2 Example of 2D-perfusion angiography pre- and post-adjustment of the double-balloon catheter of a 57-year-old female patient with hepatic metastasis from uveal melanoma and undergoing CS-PHP. **A** The venogram reveals a leakage next to the cranial balloon and resulting in (**B**) high time density values and **E** a short time to peak and a high area under the curve next to the balloon for both ROIs. **C** After balloon adjustment no leakage was detected on angiography. This was accompanied by **D** decreased time density values and a prolonged time to peak value as well as a higher area under the curve within the target ROIs (**F**). Note the increased retrograde filling of the liver veins after balloon adjustment

In contrast, the caudal balloon sees slight pressure caused by the venous blood return from the lower extremity, potentially lowering the rate of potential leakages at this site.

The 2D-PA technique is based on a reference ROI placed in the IVC and two different target ROIs. ROI1 and ROI4 were placed cap-like on top of the cranial balloon in the right atrium or adjacent to the caudal balloon. ROI2 and ROI3 were oval-shaped and placed along the equator of the balloon. To analyze the possible impact of the shape and the position we evaluated the 2D-PA values of two different ROIs at both balloon positions and compared the ROIs to each other. Furthermore, we evaluated the 2D-PA measurements for both ROIs at both balloons in a control group.

At the cranial balloon we found a significant difference when comparing the cap-like ROI1 and the ROI2 at the balloon equator after balloon adjustment. Comparable values were seen in the control group. One reason for these findings might be the cavoatrial anatomy already discussed above. Therefore, ROI2 which is placed directly next to the cavoatrial junction at the equator of the balloon might measure some contrast within the vena cava next to the balloon. Moreover, ROI2 includes parts of the balloon and the right atrial wall. Both structures underlie regular and permanent cardiac movement which is inevitable but influences the 2D-PA values [8, 12]. Therefore, a cap-like ROI outside the margin of the cranial balloon seems to be beneficial for 2D-PA.

2D-PA has the potential to assess and quantify flow of contrast agent alongside the balloons used in CS-PHP during interventions, as it determines density values to define ROIs [8, 12]. Post-processing of 2D-PA is based on conventional DSA runs and does not require additional contrast agent application or radiation exposure [8]. 2D-PA is feasible with moderate efforts and can be utilized to identify and quantify leakage of the double-balloon catheter in real time during CS-PHP. The potential of 2D-PA to quantify leakages is valuable during the procedure and also offers the opportunity to retrospectively analyze CS-PHP procedures and correlate 2D-PA values with reported side effects. Nevertheless, in the current study we focused on leakage detection and did not perform dedicated quantitative measurements.

Table 3 Comparison of the 2D-perfusion angiography parameters of ROI1 versus ROI2 and ROI3 versus ROI4 in the non-leakage control group

	ROI1	ROI2	*p* value
Cranial balloon			
PD_{tROI}/PD_{REF}	0.09 ± 0	0.16 ± 0.1	< 0.0001
TTP_{tROI}/TTP_{REF}	4.86 ± 3	5.99 ± 2.2	0.2324
AUC_{tROI}/AUC_{REF}	0.07 ± 0	0.14 ± 0.1	< 0.0001
	ROI4	ROI3	*p* value
Caudal balloon			
PD_{tROI}/PD_{REF}	0.08 ± 0.1	0.08 ± 0	0.8071
TTP_{tROI}/TTP_{REF}	5.08 ± 3.7	4.28 ± 1.8	0.4375
AUC_{tROI}/AUC_{REF}	0.07 ± 0.1	0.08 ± 0	0.2695

Mean values of the non-leakage control group in the cranial and caudal balloons

TTP = time to peak; PD = peak density; AUC = area under the curve; tROI = target region of interest; REF = reference region of interest; PD_{tROI}/PD_{REF} = ratio of the target ROI to the reference ROI for PD; AUC_{tROI}/AUC_{REF} = ratio of the target ROI to the reference ROI for AUC; TTP_{tROI}/TTP_{REF} = ratio of the target ROI to the reference ROI for TTP

As previously described for 2D-PA analysis in a broad variety of interventions, artifacts caused by movement can cause inaccurate perfusion measurement data which might be misinterpreted [8–10, 12, 18, 19]. Therefore, motion artifacts should be reduced to a minimum. In order to do so, venograms were acquired during breath-hold and pump-arrest. In addition, the different 2D-PA values for different ROIs suggest that ROI position is another important factor to consider, especially at the cranial balloon. In our study, no patient had to be excluded because of non-interpretable 2D-PA images as a result of motion artifacts.

Limitations

Our study has limitations. First, we included a relatively small number of patients with visually detectable leakages during CS-PHP at a single medical center. Our intention was to investigate the technical feasibility of 2D-PA for leakage detection of the venous double-balloon catheter. Since visually undetected leakages were not included, we were not able to demonstrate the superiority of 2D-PA for leakage detection. Nevertheless, detection of visually undetected leakages is of major importance and will be further investigated. Furthermore, due to the varying anatomy of the patients, the shape of the ROIs had to be fitted individually to each patient. This limitation of standardization might lead to inter-observer and intra-observer variability. Another limitation might be an overestimation of leakages due to different intravenous pressures during the detection venogram and the normal flow of the pump. Additionally, in our study population of 18 patients only three patients presented with a leakage at the caudal balloon. A larger study population including other high-volume centers in a multicenter study will be of value to analyze not only the feasibility of 2D-PA but also the impact of the shape and size of various ROIs.

Conclusion

2D-PA provides a feasible tool for detecting and monitoring leakages alongside the cranial portion of the double-balloon catheter used in CS-PHP. The shape and position of the ROIs used to assess perfusion and flow have an impact on the measurements.

Author's Contribution All authors significantly contributed to the design and composition, data analysis, and data interpretation for this study. Furthermore, all of the authors drafted the article or substantially revised it due to the important intellectual content. All of the authors gave their final consent for this version of the manuscript to be published.

Compliance with Ethical Standards

Conflict of interest The authors of this manuscript declare relationships with the following companies: Siemens Healthcare and ProMedicus (Bernhard Meyer and Frank Wacker, outside the submitted work). The remaining authors declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Ethical Approval Our local ethics committee approved our protocol, and written informed consent was obtained from each study patient. The study follows the ethical standards of the Declaration of Helsinki. The article includes no identifying information.

Human and Animal Rights This study follows the ethical standards of the Declaration of Helsinki. Animal studies are not part of this article (does not apply to this article).

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