iLIVER 2 (2023) 89–96

Contents lists available at ScienceDirect

iLIVER

journal homepage: www.journals.elsevier.com/iliver

Original article

The transjugular intrahepatic portosystemic shunt: Smaller stent diameters are required to optimize pressure response

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ARTICLE INFO

Keywords:
Portal hypertension
Transjugular intrahepatic portosystemic stent-shunt
TIPS
Portosystemic pressure gradient
Stent diameter
Hepatic encephalopathy
Cardiac function

ABSTRACT

Background and aims: The present treatment goal of the transjugular intrahepatic portosystemic shunt (TIPS) is a portosystemic pressure gradient of ≤12 mmHg or its reduction by >50%. This study relates the stent diameter to the reduction of the pressure gradient and attempts to predict the appropriate stent diameter necessary to reach the treatment goal.

Methods: Pressure response, super response, and poor response were investigated in 208 de-novo TIPS patients and defined as post-TIPS gradients between >6 and 12 mmHg, ≤6 mmHg, or not reaching the goal (>12 mmHg, reduction <50%), respectively. Pressures were related to the smallest stent diameters measured by planimetry of the radiographic image.

Results: Responders (65%), super responders (26%), or poor responders (9%) had comparable stent diameters of 7.2 ± 1.0 mm, but different post-TIPS gradients (9.7 ± 1.9 mmHg, 4.5 ± 1.5 mmHg, and 14.2 ± 1.4 mmHg, $p < 0.001$), relative reduction of pre-TIPS gradients (51.7 ± 11.4%, 73.6 ± 11.1%, and 34.0 ± 9.1%, $p < 0.001$), and specific reduction per mm of stent diameter (7.5 ± 2.0%/mm, 10.1 ± 2.0%/mm, and 4.8 ± 1.4%/mm, $p < 0.001$). Prediction of the stent diameter required to reach response was not possible. Only two super responders had a stent diameter of <6 mm. Super and poor responders differed by the increase in the right atrial pressure (+5.0 mmHg vs. +3.1 mmHg, $p = 0.026$) and reduction in the portal vein pressure (−8.6 mmHg vs. −4.6 mmHg, $p < 0.001$).

Conclusion: Most patients reached the treatment goal with stent diameters of <8 mm. Overtreatment (super response, gradient ≤6 mmHg) can be prevented by stent diameters as small as 6 mm. The individual response was not related to the stent diameter and not predictable. Cardiac dysfunction may play an important role by its effect on the right atrial (preload) and portal pressure (afterload).

1. Introduction

In principle, the transjugular intrahepatic portosystemic shunt (TIPS) is a side-to-side shunt bypassing portal blood through the liver into the inferior caval vein reducing portal hypertension. The diameter of the stent determines the extend of shunting and the reduction of the portal pressure as well. Unfortunately, the shunt may reduce liver perfusion, deteriorate liver function, and increase the incidence of hepatic encephalopathy [1,2]. Therefore, compared to 10 mm stents, 8 mm stents decreased the incidence of hepatic encephalopathy and improved survival [3–9].

At present, interventionalists aim at a post-TIPS portosystemic pressure gradient of ≤12 mmHg, which is widely recommended because it prevents recurrence of complications of portal hypertension effectively [10–14]. An inferior margin that addresses shunt-induced complications has not been implemented into clinical practice yet. Indeed, many patients end up with very low gradients increasing the risk of side effects without need [15–17]. As shown in these studies, occurrence of shunt-induced complications was related to a pressure gradient of <5 mmHg [15] and hepatic encephalopathy occurred almost exclusively with pressure gradients below 12 mmHg [16], or when the reduction of the pressure gradient decreased below the 50% [17]. This provides evidence that a sharp partition between effective and harmful post-TIPS pressure gradients close to a threshold of 12 mmHg and above 5 mmHg may optimize outcomes.

Two reasons may explain the low gradients often achieved and the lack of a small therapeutic window. First, the unsharp target aiming at a

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https://doi.org/10.1016/j.iliver.2023.05.004
Received 21 February 2023; Received in revised form 7 May 2023; Accepted 23 May 2023
Available online 27 May 2023

pressure gradient of ≤12 mmHg pretends that lower gradients are accepted. Second, the presently available nitinol stents do not allow controlled stent dilation at the time of placement. At de-novo TIPS implantation, adjustment of a specified pressure gradient is difficult due to the low compliance of the cirrhotic liver and the unpredictable behavior of the nitinol stent. As shown previously, both early (at intervention) and late stent diameters differ considerably from what is expected [18–22]. At TIPS implantation, dilation of nitinol stents with a 10 mm balloon resulted in a true stent diameter of only 8.2 ± 0.9 mm and expanded during follow-up to 9.8 ± 0.7 mm [18] suggesting a further reduction of the pressure gradient during early follow-up.

The aim of this study was to relate the stent diameter to the pressure gradient achieved at the end of the TIPS procedure and to evaluate predictive variables of the stent diameter needed to achieve the treatment goal, a gradient of ≤12 mmHg or a reduction of the gradient by ≥50%. The stent diameter is defined as the smallest diameter determined by planimetric measurement after balloon dilation of the stent. According to the law of Hagen–Poiseuille, the smallest diameter determines the flow while the length of the smallest segment or of the stent does not contribute much.

2. Methods

This monocenter, observational study was designed prospectively and performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our University Hospital (Number: 580/19); Clinical trial number: 580/19. The study was investigator-initiated without any sponsorship. Informed consent for TIPS implantation was obtained from all patients.

The study included 231 consecutive patients receiving de-novo TIPS implantation between June 2016 and December 2020. Twenty-three patients were excluded because of portal vein thrombosis (17 patients), noncirrhotic portal hypertension (4 patients), or uncomplete data (2 patients). Just before the intervention, the portal vein flow velocity (V_{max}) was determined by Duplex sonography from a ventral and intercostal plane. Patients were then prepared, sedated, and monitored to use intravenous propofol and midazolam. No mechanical ventilation was supplied.

The puncture of the portal vein was performed under transcutaneous sonographic guidance from a right lateral intercostal view [1,23]. After successful puncture of a portal vein branch, a 0.035″ hydrophilic curved guide wire was advanced into the splenic vein. To exclude mispuncture of a biliary duct or a branch of the hepatic artery, the needle track was opacified by 5–10 mL of diluted contrast, injected per hand into the upper part of the track.

Two different brands of stents were implanted: 111 patients received the Viatorr CX stent (Viatorr® Controlled Expansion, Gore, Flagstaff, USA) and 97 patients received a BeGraft peripheral stent (Bentley, Hechingen, Germany). The Viatorr CX stent can be dilatated to diameters of 8–10 mm. The balloon expandable BeGraft peripheral is mounted on an 8 mm balloon catheter. It was used to keep the opportunity of a smaller diameter of 6 or 7 mm [24,25].

If a Viatorr CX stent was chosen, the track was dilated, a 10 F sheath (length 45 cm, Cook Medical Europe, Limerick, Ireland) was advanced into the main portal vein, and the Viatorr CX introduced and released. The stent was dilated to 8 mm to achieve a reduction of the pressure gradient by >50% or ≤12 mmHg. In patients showing insufficient response, further dilation to 9 or 10 mm was performed when desired. If a BeGraft peripheral was chosen, the stent was introduced and dilated without the need of prior dilatation of the needle track or placement of a long sheath. The pressure gradient was measured, and dilatation was repeated until the desired pressure gradient was adjusted. Finally, angiography was performed to document shunt anatomy and to confirm shunt patency.

Portal venography and pressure measurements were performed in the portal vein and the right atrium as described previously [26]. An electronic device (Infinity ® Acute Care System, Dräger, Lübeck, Germany) was used, and the pressures were recorded after achieving a horizontal line for at least 1 min. Radiographs of the stent were performed and the diameters were determined by planimetry using the IMPAX-Software (AGFA IMPAX EE R20 XV SU3, Agfa HealthCare NV - Mortsel, Belgium). The smallest diameter of the stent was measured because it determines the hemodynamic effect of the shunt. In addition to the stent diameter, the diameter of the portal vein was measured half way between the confluence and the bifurcation (Fig. 1).

2.1. Study endpoints and definitions

The study endpoint was the smallest stent diameter and the respective portal and right atrial pressures achieved at the end of the TIPS procedure. To predict the stent diameter necessary to achieve the treatment goal, physical variables such as portal vein and right atrial pressures, portal vein diameter, portal vein flow velocity, and hepatic resistance were measured before the stent placement. The treatment goal was defined as a post-TIPS pressure gradient of ≤12 mmHg or a reduction of the gradient by ≥50%. Patients who reached the goal and who had a portoatrial pressure gradient between >6 mmHg and 12 mmHg are defined as responders. Patients who had a portoatrial pressure gradient after TIPS of ≤6 mmHg are termed as super responders. The inferior margin of 6 mmHg was chosen because it allows sufficient pressure reduction in patients with a baseline pressure gradient of 12 mmHg, the lowest value accepted for the TIPS intervention. Patients not achieving the goal are defined as poor responders. The relative reduction of the pressure gradient is calculated as (gradient before TIPS-gradient after TIPS/gradient before TIPS)*100%. The specific reduction of the pressure gradient is the relative reduction divided by the stent diameter.

The portal vein flow was calculated as flow = $\pi\ d^2/4\ V_{mean} = \pi\ d^2/4\ V_{max}/2$, where the diameter d of the portal vein was determined by planimetry of the angiography. V_{max} is the average of 2 duplex-sonographic measurements, one from an intercostal and one from a ventral plane. The vascular resistance of the liver is calculated as R = ΔP/flow, where ΔP is the pressure in the portal vein minus the pressure in the right atrium.

2.2. Statistical analyses

Continuous variables are expressed as mean with standard deviation and the corresponding range, whereas categorical variables are reported as frequencies and percentages. For continuous variables, differences were determined using Wilcoxon-Mann-Whitney and Kruskal–Wallis tests as there was no Gaussian distribution of the data, confirmed by the Kolmogorov–Smirnov test. χ^2 tests, or Fisher exact tests were used for categorical variables. Correlations between two variables were determined using the Spearman's rank correlation test. P values of <0.05 were considered as being significant. In case of multiple testing, correction of the p value according the Bonferroni method was applied.

3. Results

The characteristics of the patients included in the study are depicted in Table 1. Most patients had alcoholic cirrhosis (66%), followed by viral hepatitis (10%) and nonalcoholic steatohepatitis (6%) and received the TIPS intervention for treatment of refractory ascites.

Overall, 189 patients (91%) achieved the treatment goal of either a post-TIPS pressure gradient of ≤12 mmHg (181 patients) or a relative reduction of the pre-TIPS gradient by ≥50% (7 patients with very high pre-TIPS gradients). Response (gradient between >6 and 12 mmHg) was seen in 136 patients (65%) and super response (gradient ≤6 mmHg) in 53 patients (26%). Nineteen patients (9%) did not reach the treatment goal (poor response). The biomedical characteristics of the groups were comparable (Table 1). The hemodynamic variables before the TIPS implantation are depicted in Table 2. The portal vein flow was 634 ml/min. A minority of five patients had stagnant or retrograde portal vein flow.

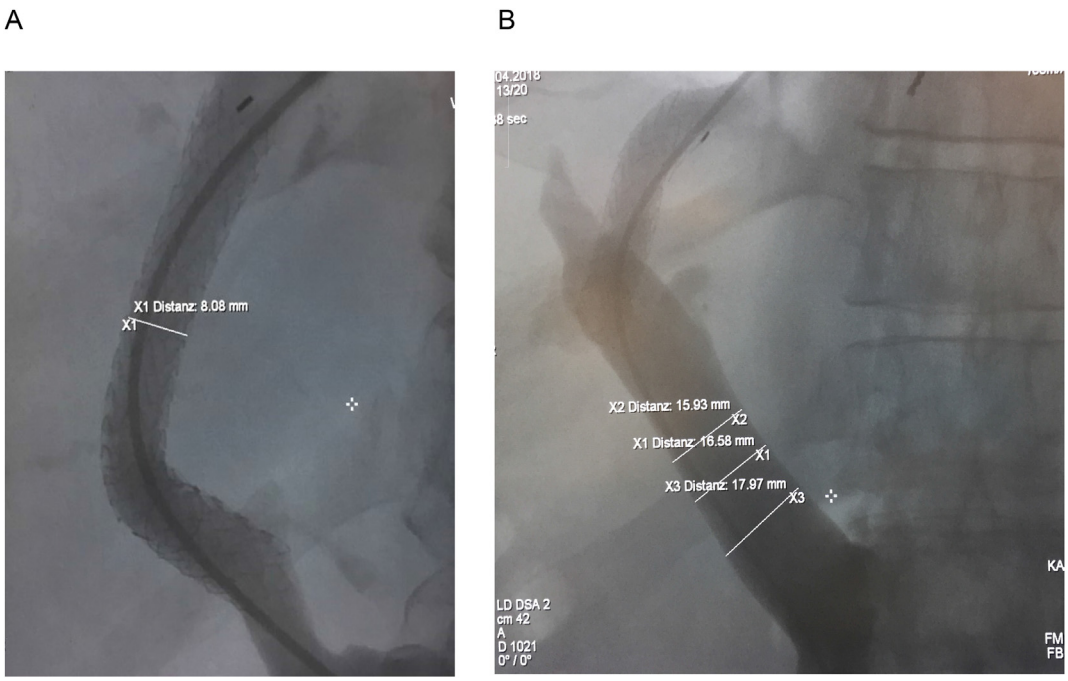

Fig. 1. Planimetric measurement of (**A**) the smallest stent diameter and (**B**) the portal vein diameter half way between the confluence and the bifurcation.

All variables were similar between groups, except the pressure gradient which was lower in patients showing super response ($p = 0.008$).

Stent implantation resulted in a considerable reduction of the pressure gradient by 55.6%. This was achieved with a mean stent diameter of only 7.2 mm. The distribution of pressure gradients and stent diameters is shown in Fig. 2A and B. Pressure gradients and stent diameters showed great variability ranging from 0 to 18 mmHg and from 4.2 to 9.8 mm, respectively. The majority of 174 patients (84% of all patients) had a stent diameter of <8 mm and 77% of patients reached the treatment goal with a stent diameter of <8 mm. 68 patients (33%) had a diameter of <7 mm, and 23 patients (11%) a diameter of <6 mm. Only 34 patients (16%) had a stent diameter of ≥8 mm. The pressure gradients were not different between groups with smaller or larger stent diameters (Fig. 3). In total, 111 patients receiving a Viatorr CX stent dilated with an 8 mm balloon had a smallest stent diameter of 6.8 ± 1.0 mm (median 6.9; range 3.8–7.9 mm). BeGraft stents were dilated under fluoroscopic vision without always fully expanding the 8 mm balloon.

As shown in Table 3 and Fig. 4, responders, super responders, and poor responders differed remarkably with respect to the effect of the shunt although stent diameters were comparable. As per definition, compared to responders, super responders had a significantly lower post-TIPS porto-atrial pressure gradient which may partially be caused by a greater reduction of the portal vein pressure (Δ portal vein pressure). In addition, both the relative (51.7% vs. 73.6%) and specific (7.5%/mm vs. 10.1%/mm) reduction of the pre-TIPS pressure gradient differed significantly. Comparing super responders with poor responders, significant differences were seen in all parameters except the stent diameter. In particular, TIPS led to a higher increase in the right atrial pressure (Δ right atrial pressure) and a greater decrease in the portal vein pressure (Δ portal vein pressure). These changes are the underlying cause of the great difference in the post-TIPS pressure gradients (4.5 mmHg vs. 13.9 mmHg), and in the relative (73.6% vs. 34.0%) and specific reduction of the gradients (10.1 vs. 4.8%/mm stent diameter). As a consequence of the small pressure gradient, super responders had a lower hepatic resistance than poor responders. It is important to state, that only two super responders (4%) had stent diameters of <6 mm implicating, that smaller diameters are not required to prevent super response.

Table 1
Baseline characteristics of patients.

	All patients $N = 208$	Responder $n = 136$	Super responders $n = 53$	Poor responders $n = 19$
Age (*Mean* ± *SD*)	61 ± 12	61 ± 13	60 ± 12	63 ± 10
Gender, male/female, *n* (%)	142/66 (68.3/31.7)	92/44 (67.6/32.4)	34/19 (64.2/35.8)	16/3 (84.2/15.8)
TIPS-indication, *n* (%)				
- variceal bleeding	63 (30.3)	41 (30.1)	20 (37.,7)	2 (10.5)
- refractory ascites	145 (69.7)	95 (69.9)	33 (62.3)	17 (89.5)
Laboratory data (*Mean* ± *SD*)				
- bilirubin, (mg/dL)	1.6 ± 1.4	1.7 ± 1.5	1.5 ± 0.8	1.9 ± 1.6
- creatinine (mg/dL)	1.4 ± 0.8	1,4 ± 0.8	1.3 ± 0.8	1.5 ± 0.9
- INR	1.2 ± 0.2	1,2 ± 0.2	1.2 ± 0.2	1.2 ± 0.2
- albumin (g/dL)	3.2 ± 0.7	3.2 ± 0.6	3.4 ± 0.8	3.3 ± 0.7
- platelets ($\times 10^3$)	140 ± 100	145 ± 111	122 ± 79	152 ± 58
MELD score (*Mean* ± *SD*)	13 ± 5	13 ± 5	12 ± 5	14 ± 6
Child-Pugh class, *n* (%)				
A	38 (18.3)	20 (14.7)	16 (30.2)	2 (10.5)
B	133 (63.9)	93 (68.4)	27 (50.9)	13 (68.4)
C	37 (17.8)	23 (16.9)	10 (18.9)	4 (21.1)

NASH: nonalcoholic steatohepatitis.
MELD: model of end stage liver disease.

Table 2
Hemodynamic variables before TIPS-implantation of all patients and of responders, super responders, and poor responders. Values are *means* ± *SD* (median; range).

	All patients $N = 208$	Responders $n = 136$	Super responders $n = 53$	Poor responders $n = 19$
Before TIPS				
Portal vein flow velocity (cm/sec)	15.4 ± 6.0 (15; 0–40)	15.5 ± 6.1 (15.0; 0–35)	15.4 ± 6.6 (15; 4–35)	15.2 ± 8.3 (12; 8–40)
Portal vein diameter (mm)	13.0 ± 2.8 (12.9; 6.7–22.5)	12.8 ± 2.7 (13.0; 6.7–22.5)	13.0 ± 3.0 (12.5; 7.5–22.0)	14.3 ± 2.8 (13.5; 10.7–21)
Portal vein flow (mL/min)	634 ± 372 (552; 0–2145)	623 ± 369 (549; 0–2146)	633 ± 373 (597; 105–2052)	705 ± 395 (567; 290–1563)
Right atrial pressure (mmHg)	5.0 ± 4.2 (4; −3–21)	4.9 ± 4.4 (4; −3–20)	5.3 ± 4.3 (5; −3–21)	4.7 ± 3.5 (4; 0–14)
Portal vein pressure (mmHg)	25.3 ± 6.2 (25; 12–46)	25.7 ± 6.3 (25; 16–46)	23.6 ± 5.9 (23; 12–39)	26.6 ± 5.9 (25; 18–40)
Pressure gradient (mmHg)	20.3 ± 5.3 (20; 8–45)	20.8 ± 5.3 (20; 10–45)	18.3 ± 5.0 (18; 8–32)[a]	21.9 ± 4.1 (21; 16–32)[b]
Hepatic resistance ($dyne^{a}sec^{a}cm^{-5}$)	3607 ± 2891 (2782; 655–22646)	3705 ± 2853 (2859; 655–20170)	3437 ± 3279 (2565; 830–22646)	3393 ± 1900 (3096; 972–7319)

[a] Super responders vs. responders: $p = 0.008$.
[b] Super responders vs. poor responders: $p = 0.008$.

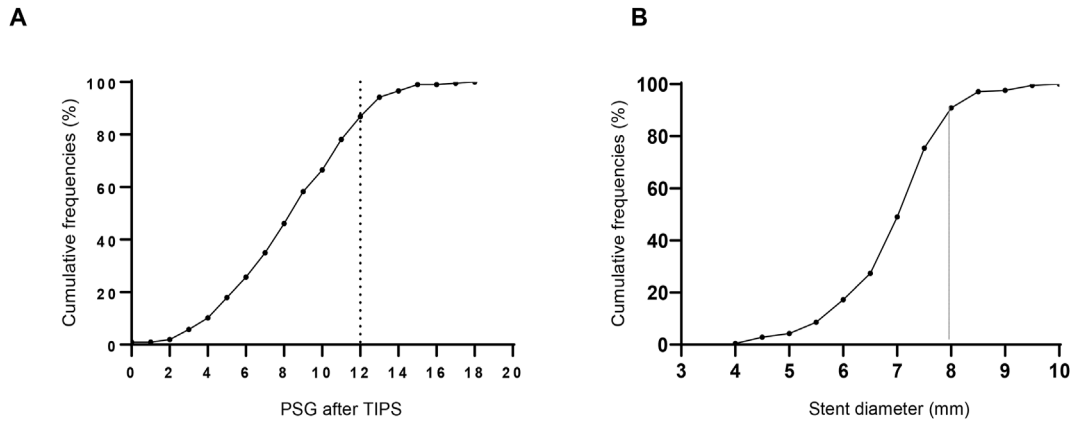

Fig. 2. (A) Cumulative frequency analysis of the post-TIPS pressure portosystemic gradient (PSG) of the 208 patients. Ninety-one percent of patients had a post-TIPS gradient of ≤12 mmHg (B) Cumulative frequency analysis of the smallest stent diameters measured by planimetry.

Raising the threshold to 14 mmHg and the inferior margin to 7 mmHg would result in a lower proportion of poor responders (12 pts, 6%) and a higher proportion of super responders (72 pts, 35%). In contrary, a threshold of 10 mmHg and an inferior margin of 5 mmHg would result in a higher proportion of poor responders (64 pts, 31%) and a lower proportion of super responders (37 pts, 18%).

Our study demonstrates very limited correlations between the smallest stent diameter and the pre-TIPS variables such as the portal vein flow velocity ($r = -0.245$), the portal vein diameter ($r = 0.012$), the portal vein flow ($r = -0.040$), the portoatrial pressure gradient ($r = 0.118$), and the hepatic resistance ($r = 0.057$). This is also true for the correlation of the smallest stent diameter with the post-TIPS pressure gradient ($r = -0.075$) and the relative reduction in the pressure gradient ($r = 0.141$).

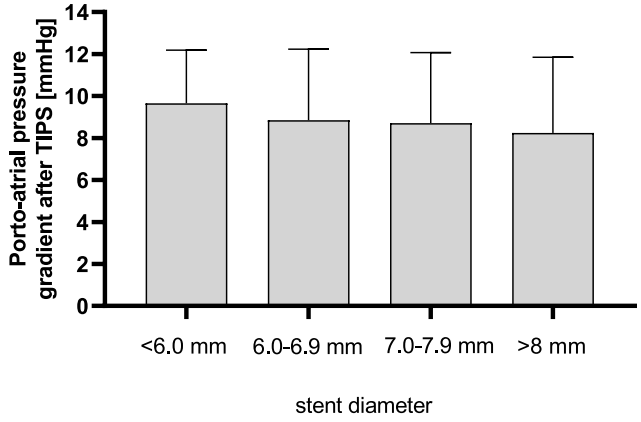

Fig. 3. Porto-atrial pressure gradients (mmHg) obtained with different stent diameters (*means* ± *SD*). No significant difference between the various diameters.

4. Discussion

It is a teleological fact that shunt-induced complications depend on stent diameter that defines the reduction of the portosystemic pressure gradient. In addition to the shunt, many pre- and post-TIPS variables have been identified to trigger or predict HE after TIPS [27]. The role of the stent diameter has been addressed by comparing 8 mm with 10 mm stent diameters. One randomized [3] and four retrospective [4–7] studies showed a positive effect of the smaller diameter on HE without a difference in the rate of rebleeding. With respect to survival, two of the five studies did not find a survival benefit of the 8 mm group [3,7], while 3 studies did [4–6]. In contrast, a randomized study showed an increased rate of rebleeding with 8 mm stents, the reason why the study was closed preterm [28]. Two meta-analyses including five and seven studies stated that 8 mm stents may be recommended as they can reduce the risk of post-TIPS-HE [8,9]. The smaller stents did not worsen rebleeding but may lead to an increased rate of shunt dysfunction. Survival was improved in one [8] but not the other meta-analysis [9]. Overall, 8 mm stents may be recommendable in the routine use.

Our study shows that 91% of the patients achieved the treatment goal. Seventy-seven percent of whom had a (true) stent diameter of <8 mm. Defining a post-TIPS pressure gradient of ≤6 mmHg as inferior margin to prevent overtreatment, 26% of patients fell below. Compared to responders, these super responders had similar stent diameters but a higher specific reduction of the gradient indicating an exceptional response to the shunt. Only two of the super responders had a stent diameter of <6 mm demonstrating that a diameter of 6 mm is sufficiently small to safely prevent from overtreatment. As also shown in this study, a small number of patients (9%), termed as poor responders, did not reach the

Table 3
Hemodynamic variables after TIPS-implantation obtained in all patients, responders, super responders, and poor responders. Δ right atrial and Δ portal vein pressures are the differences between pressures measured before and after TIPS-implantation. Values are *means* ± *SD* (median; range).

	All patients $N = 208$	Responders $n = 136$	Super responders $n = 53$	Poor responders $n = 19$	p value Super vs responders	p value Super vs poor	p value responders vs poor
After TIPS							
Right atrial pressure (mmHg)	9.2 ± 4.7 (9; −3–25)	9.0 ± 4.9 (9; −3–24)	10.3 ± 4.3 (9.5; 4–25)	7.8 ± 3.7 (8; 2–16)	0.787	0.150	0.381
Δ right atrial pressure (mmHg)	4.2 ± 3.1 (4; −6–17)	4.1 ± 3.2 (4; −6–17)	4.95 ± 2.9 (4; −2–15)	3.1 ± 2.5 (2; 0–9)§	0.362	0.026	0.146
Portal vein pressure (mmHg)	18.1 ± 5.3 (18; 7–32)	18.8 ± 5.1 (19; 9–32)	15.1 ± 4.7 (14.5; 7–31)	22.0 ± 4.1 (21; 16–30)	<0.001	<0.001	0.025
Δ portal vein pressure (mmHg)	7.2 ± 4.1 (7; −3–24)	7.0 ± 4.0 (6; −3–24)	8.6 ± 4.4 (9; 2–19)	4.6 ± 2.8 (4; 0–11)§§	0.017	<0.001	0.054
Pressure gradient (mmHg)	8.8 ± 3.3 (9.0; 0–18)	9.7 ± 1.9 (9.5; 7–15)	4.5 ± 1.5 (5; 0–6)	14.2 ± 1.4 (14; 13–18)	<0.001	<0.001	<0.001
Relative reduction of gradient (%)	55.6 ± 16.0 (55; 14.3–100)	51,7 ± 11.4 (53; 14.3–75)	73.6 ± 11.1 (74.5; 50–100)	34.0 ± 9.1 (32; 18.8–48.1)	<0.001	<0.001	<0.001
Diameter of stent (mm)	7.2 ± 1.0 (7.3; 4.2–9.8)	7.0 ± 1.0 (7.2; 4.2–9.6)	7.4 ± 0.9 (7.4; 4.7–9.8)	7.1 ± 0.9 (7.2; 5.2–8.7)	0.999	0.395	0.999
Specific reduction of gradient (%/mm)	7.9 ± 2.4 (7.8, 2.0–15)	7.5 ± 2.0 (7.4; 2.0–13.6)	10.1 ± 2.0 (9.8; 6.5–15.4)	4.8 ± 1.4 (4.6; 2.5–7.8)	<0.001	<0.001	<0.001
Hepatic resistance (dyne*sec*cm^{-5})	441 ± 342 (360; 76–2248)	488 ± 284 (408; 172–1560)	256 ± 125 (216; 76–507)	774 ± 750 (352; 161–2087)	<0.001	0.009	0.999

treatment goal. This was partially due to the fact that investigators decided against further stent dilation to avoid shunt-induced complications. Again, these patients had similar diameters compared to responders but a lower relative and specific reduction of the gradient indicating a limited response to the shunt.

The portosystemic pressure gradient is determined by its two components, the atrial and the portal pressure. The atrial pressure is closely related to the cardiac preload. After having bypassed the vascular bed of the liver by the TIPS, the portal pressure depends mainly on the cardiac afterload, which is related to the mean arterial pressure. Together with the splanchnic/splenic vascular resistances, it determines the portal inflow and pressure. It can be assumed that the lower the mean arterial pressure and the higher the central venous pressure the lower is the gradient after TIPS, and vice versa. This clearly suggests that cardiac function decides on pressure response.

Opening of the TIPS may be regarded as a stress-test unmasking cardiac dysfunction. This may, in particular, be true for patients showing super response. Their very low gradients are due to an inadequate increase in the central venous pressure (preload) and low splanchnic blood supply (reduced afterload). In contrast, poor response may occur in patients with a low cardiac preload and/or a high afterload indicating good cardiac function. This is confirmed by the findings in poor responders of a greater pre-TIPS portal vein flow in the presence of a higher portal vein pressure and greater portoatrial pressure gradient. In contrast, super responders had a lower pre-TIPS pressure gradient indicating decreased afterload. With respect to post-TIPS variables, super responders showed a higher increase in the right atrial pressure and greater decrease in the portal vein pressure also supporting the hypothesis. In contrast to our super responders receiving relatively small shunts, low post-TIPS gradients may also be seen in patients with good cardiac function receiving wide stents. These patients may differ by their high blood flow through the shunt, while super responders are expected to have a low blood flow. A recent study investigating predictive factors of cardiac decompensation showed that 20% of patients developed cardiac decompensation after TIPS [29]. The patients had post-TIPS pressure gradients of only 5 ± 2 mmHg after the implantation of 10 mm stents [29]. Cardiac decompensation was not related to Child-Pugh or MELD scores, etiology, or active alcohol consumption. In another small study, 0.9% of patients ($n = 8$) developed symptomatic heart failure 1–7 days after TIPS [30]. Similar to our study, the increase in the right atrial pressure by the TIPS was significantly greater in the small group of patients developing cardiac decompensation.

With respect to shunt hemodynamics, the low gradient of super responders may result in a low blood flow through the shunt while poor responders may have a high shunt blood flow due to the relatively high pressure gradient. Similar is true for hepatic hemodynamics. Due to the low sinusoidal-atrial gradient, super response may be accompanied by a low hepatic perfusion depending on the arterial blood supply. In addition, the lower the portoatrial gradient the greater is the proportion of retrograde flow in the sinusoids, a situation which may, together with the decreased flow, contribute to reduced metabolic function, e.g. glutamine synthesis.

Little is published about the relevance of an inferior margin. Our definition is supported by the American Society of Interventional Radiology recommending that the portosystemic gradient after TIPS should not be <5 mmHg [31]. This is confirmed by a retrospective study showing that medically uncontrolled shunt-induced complications occurred exclusively in patients with a post-TIPS pressure gradient of ≤5 mmHg [15]. Surprisingly, a retrospective study could not find a difference in HE in patients with post-TIPS gradients above or below 5 or even 8 mmHg [32]. The finding is of questionable quality since groups were not characterized and not matched. A recent retrospective study including patients with refractory ascites showed that patients with a greater pressure reduction (>60%) and a mean post-TIPS gradient of 7 mmHg had a better 6-week ascites control and survival than patients with a reduction by <60% and a mean post-TIPS gradient of 8 mmHg [33]. The 6-week incidence of overt HE was uncommonly low (3% and 1%) and similar between groups. The study may indicate that ascites patients need low pressure gradients but a critical lower margin has not been investigated.

As also shown in this study, prediction of the diameter to avoid gradients of ≤6 mmHg and to obtain a pressure gradient of >6 mm is not possible and, therefore, stepwise dilation beginning with a 6 mm balloon is recommended. The general use of 8 mm stents is not sufficiently protective since most super responders had diameters of <8 mm. In addition, poor responders may benefit from greater diameters to reach the treatment goal possibly without having a greater risk of pressure related complications. To create even smaller shunts than 8 mm underdilation of 8 mm or 10 mm stents using a 6 mm balloon has been performed [20,34,35]. The study by Schepis et al. [34] compared patients with 8–10 mm stents dilatated with 8 mm or 10 mm balloons with patients receiving underdilated shunts using 6 mm or 7 mm balloons. Underdilation reduced HE significantly (27% vs. 54%). Rebleeding or recurrence of ascites did not differ and no TIPS occlusion was observed. The authors state that, during a mean follow-up of 252 days, none of the PTFE stents

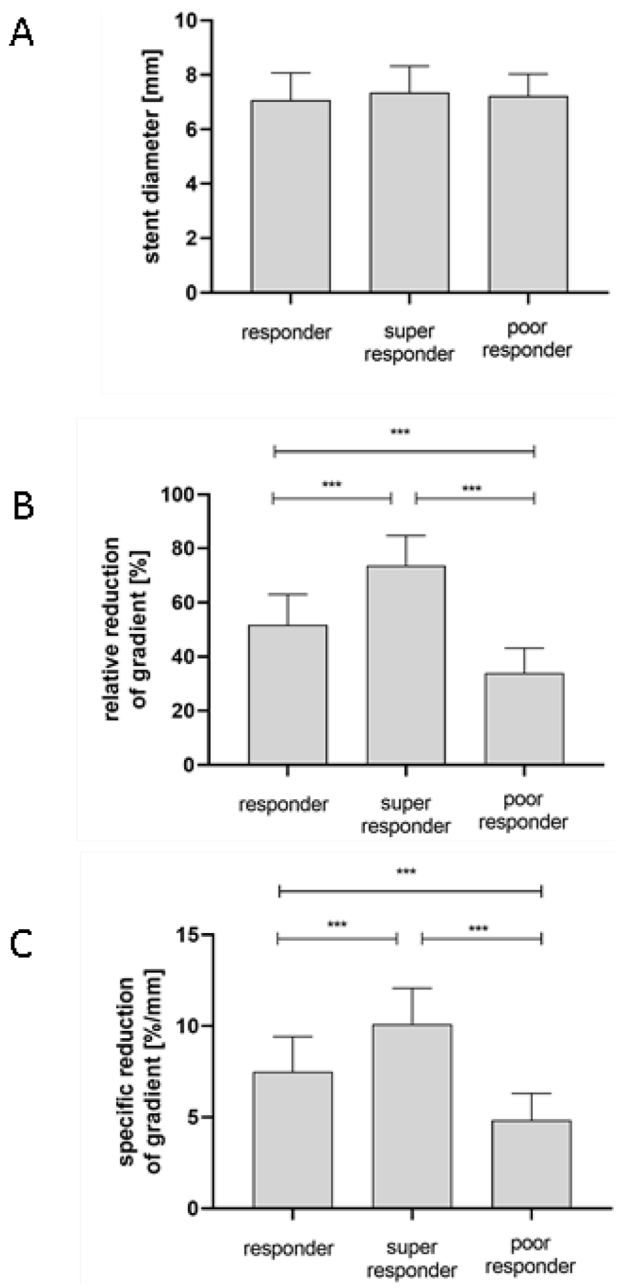

Fig. 4. **A**: Stent diameters, **B**: relative and **C**: specific reduction of the pressure gradients of patients with response (post-TIPS gradient between >6 and 12 mmHg), super response (post-TIPS gradient ≤6 mmHg), and poor response (post-TIPS gradient >12 mmHg or reduction <50%). *** indicate a significance between groups in relative (panel B) and specific reduction (panel C) of the portosystemic pressure gradient with a *p*-value of <0.001.

self-expanded to the nominal diameter. The case control study by Liu et al. [35] compared patients whose stents were dilated with a 6 mm or 8 mm balloon. Compared to the 8 mm group, the 3-month incidence of HE was significantly reduced in the underdilated group (11% vs. 29.5%). Variceal rebleeding, shunt dysfunction, and survival were not different. Surprisingly, pressure gradients before and after TIPS were almost identical between groups assuming that stent diameters did not differ considerably. CT scan after 3 months demonstrated expansion of all stents to a diameter of 8 mm. According to these studies, underdilation may be recommended as a routine strategy to improve short-term HE rates after TIPS. However, both studies are retrospective and harbor several inconsistencies. Self-expansion of the stent toward its nominal diameter has been seen by Liu but not by Schepis although both groups used CT to determine the stent diameter. In addition, Liu et al. found similar pressure gradients after TIPS, a finding which is not compatible with different stent diameters. The explanation comes from findings of this study and from a recent study investigating the effect of the balloon size on the stent diameter measured during the intervention [18]. Smallest diameters of the nitinol stents were similar irrespective whether 8 mm, 9 mm, or 10 mm balloons were used suggesting that, at TIPS implantation, the compliance of the surrounding tissue determines the diameter rather than the size of the dilatation balloon. For sure, the diameters of the balloon and the stent differ substantially. With respect to self-expansion of the nitinol stents, the finding by Schepis et al. [34] is not in accordance with many other studies including the study by Liu et al., showing that self-expansion of the stent toward its nominal diameter occurs within several days or weeks already [19–22]. In contrast to the studies by Schepis et al. [34] and Liu et al. [35], the study by Gaba et al. [20] found rapid enlargement of the underdilated stent and no reduction in the incidence of HE.

Another approach to create smaller than 8 mm shunts is constraining the Viatorr stent by an outer balloon expandable metallic stent. Four very small studies implanting constrained stents, dilated with a 6 mm balloon, have been published recently [36–39]. They show technical feasibility, lower incidence of HE, higher post-TIPS pressure gradients, a greater need for revision, and higher incidence of treatment failure. Data on long-term outcomes are missing. All patients were left with 6 mm shunts and a stepwise dilation to achieve the treatment goal was not pursued. Clearly, a general use of 6 mm shunts is not advisable and should be restricted to the subgroup of patients showing super response. The recommendation to generally create 6 mm shunts and complement the insufficient fall in the pressure gradient with drugs if necessary [40] may not be advisable either. These drugs are likely to decrease the arterial hepatic perfusion leading to an increased incidence of hepatic encephalopathy. In contrast, further dilation of the TIPS to a degree which is needed to resolve the clinical problem may not deteriorate but even improve hepatic arterial perfusion by activating the hepatic arterial buffer response and should, therefore, be preferred. Overall, underdilation or stent constriction may be reasonable tools to reduce HE. Whenever nitinol stents are used, underdilation is of temporary value. It does not allow sustained individual tuning at the time of stent placement. In contrast, the use of a constraining stent may allow a stepwise adaptation of the stent diameter to achieve the treatment goal and to prevent overtreatment/super response. An alternative to this technique may be the use of a balloon-expandable, covered metallic stent as described previously [24,25] and practiced in almost half of the patients of this study. According to our results, the constraining technique or the exclusive use of a balloon-expandable metallic stent may be recommended until new nitinol stents are available permitting stepwise dilation from 6 to 10 mm.

The results of our study may be limited by the accuracy of the planimetric measurement. The method has been validated previously by our group by comparing the largest measured diameter at the stent endings with the nominal diameter of the stent. Pearson correlation between measured and nominal values were excellent ($r = 0.952$, $p < 0.001$) with interclass correlation coefficients of 0.976 [95% CI: 0.964–0.984] and 0.975 [0.964–0.984] for absolute agreement and for consistency, respectively. This demonstrates that radiological/planimetric measurements are accurate [18]. Second, the measurement of the pressure gradient and factors influencing the gradient may affect results. We measured pressures in the portal vein and the right atrium and not in the hepatic or inferior caval vein. This may result in a systematic error of +2 mmHg when compared to the measurement in the inferior caval vein [26]. On the other hand, propofol sedation may reduce the gradient substantially. Our previous measurements before the availability of propofol consistently showed portoatrial gradients of 24 mmHg [23], a difference to the actual measurements of −3 mmHg. This is in accordance with a recent study showing that propofol reduced the gradient by 2 mmHg [41]. Thus, the effects of using the right atrium as a reference

level and applicating propofol are almost neutralizing and justify adherence to the previously determined 12 mm Hg threshold [42]. As demonstrated, applying a threshold of 14 mmHg (measurement in the right atrium without deep sedation) and a lower margin of 7 mmHg (50% of the threshold) would decrease the number of poor responders slightly and increase the proportion of super responders. In contrary, applying a threshold of 10 mmHg (measurement in the inferior caval vein with deep sedation) would increase the number of poor responders but decrease the proportion of super responders. In any case, super response and poor response remain a substantial problem independent from the location of the pressure measurement. Third, pressures obtained at TIPS implantation may change during follow-up limiting the relevance of the measurements at implantation. However, measurements in the pre-Viatorr era showed no difference of the gradients measured at TIPS implantation and 2 months later [43]. Using the Viatorr stent, measurements at TIPS implantation and early after TIPS (about 1 day) showed poor correlation ($r = 0.34$, $p = 0.041$) when patients were intubated and ventilated [44]. In awake patients, gradients dropped by 1.5 mmHg within 1–2 days and remained stable during 1 month of follow-up [44]. Another study on patients receiving general anesthesia showed an increase of the pressure gradient of 2.6 mmHg during 48 h after the TIPS implantation [45]. A recent study published in abstract form showed no difference of the gradients determined shortly (24–72 h) or late (1 months) after TIPS [46]. At the end, results of pressure measurement during follow-up are controversial. Excluding general anesthesia, studies showed slight decreases or no change of the gradients measured at TIPS implantation and later on. Independent from follow-up pressures, our findings have their own implication by unmasking cardiac dysfunction in a very early stage. Finally, our study is limited to physiological variables obtained during the TIPS-intervention. It does not consider clinical follow-up parameters.

In summary, our study shows that most patients responded to the TIPS treatment reaching the treatment goal with (true) stent diameters between 6 mm and 8 mm. In general, diameters do not correlate with pressure gradients and cannot be predicted by pre-TIPS hemodynamic variables. This does not conflict with the fact that, in an individual case, the pressure response depends on the diameter: a greater stent diameter leads to a greater reduction of the gradient. A specific gradient, however, can be achieved with a stent diameter of 6 or 12 mm depending on individual conditions. Opening of the stent may demask cardiac dysfunction which explains the different response to the TIPS. The creation of 6 mm shunts and gradual dilatation if necessary is recommended to prevent excessive pressure reduction (super response) which may have negative cardiac and hepatic consequences. Further studies are required to predict and prevent super response and to relate response to outcomes.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

MR: design of study, performing TIPS procedures, data collection, writing of manuscript. DB: statistics, writing of manuscript, TIPS procedure. RT: writing of manuscript, supervision, MS: design of study, performing TIPS procedures, data collection, writing of manuscript design of study, performing TIPS procedures, data collection, writing of manuscript.

Acknowledgments

None.

Declaration of competing interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.financial support.

Data available statement

The data used in this study are available upon request from the corresponding author.

Ethics statement

This mono-centerre, observational study was designed prospectively and performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our University Hospital (Number: 580/19). The study was investigator-initiated without any sponsorship. Informed consent for TIPS implantation was obtained from all patients.

Informed consent

Informed consent was obtained from each patient.

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