ORIGINAL RESEARCH

Laser speckle contrast imaging for quantitative assessment of facial flushing during mesenteric traction syndrome in upper gastrointestinal surgery

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Abstract

The mesenteric traction syndrome (MTS) is associated with prostacyclin (PGI_2) facilitated systemic vasodilatation during surgery and is identified by facial flushing. We hypothesized that severe facial flushing would be related to the highest concentrations of plasma PGI_2 and accordingly to the highest levels of skin blood flow measured by laser speckle contrast imaging (LSCI). Patients scheduled for major upper abdominal surgery were consecutively included. Within the first hour of the procedure, facial flushing was scored according to a standardized scale, and skin blood flow (LSPU) was continuously measured on the forehead and the cheeks by LSCI. Arterial blood samples for 6-keto-$PGF_{1\alpha}$ (stable metabolite of PGI_2) and hemodynamic variables were obtained at defined time points. Overall, 66 patients were included. After 15 min of surgery, patients with severe flushing demonstrated the highest plasma 6-keto-$PGF_{1\alpha}$ concentration and the most significant decrease in systemic vascular resistance. Accordingly, the skin blood flow on the forehead (238 [201–372] to 562 LSPU [433–729]) and the cheeks (341 [239–355] to 624 LSPU [468–917]) increased and were significantly higher than for patients with moderate or no flushing (both, P = 0.04). A cut-off value for skin blood flow could be defined for both the cheeks and the forehead for patients with severe flushing vs. no flushing (425/456 LSPU, sensitivity 75/76% and specificity 80/85%). MTS is linked to an increase in facial skin blood flow during upper gastrointestinal surgery. By applying LSCI, it is possible to quantitatively register facial blood flow, and thereby provide an objective tool for intraoperative verification of MTS.

Keywords Mesenteric traction syndrome · Skin blood flow · Facial flushing; prostacyclin · Laser speckle contrast imaging

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1 Introduction

During abdominal surgery, manipulation of organs and traction on the mesentery may lead to increased shear stress on endothelial cells of the mesenteric vessels stimulating the production of prostacyclin (PGI_2) facilitated by activation of cyclooxygenase (COX)-1 [1–4]. The release of PGI_2 initiates universal vasodilatation being responsible for a triad of facial flushing, hypotension, and tachycardia, which has classically defined the mesenteric traction syndrome (MTS) [3–6]. Thus, the occurrence of MTS may cause hemodynamic instability and thereby increase the risk of organ hypo-perfusion if not promptly identified.

MTS is a relatively unknown entity among surgeons, even though an incidence of 30–85% is reported during open abdominal surgery, albeit lower for minimally invasive procedures [1, 7]. An explanation for this may be that PGI_2 analyses are not readily available during surgery and

that clinical symptoms such as facial flushing may be overlooked or misinterpreted as facial flushing is a subjective evaluation based on opinions of the involved staff. Also, intraoperative hypotension and tachycardia can be attributed to other factors, e.g. induction of anesthesia or activation of epidural analgesia [8]. The presence of facial flushing is a key symptom for detecting MTS and attempts have been made to grade the clinical appearance according to a standardized scale [1]. Facial flushing during MTS is likely due to increased blood flow in the forehead and the cheeks, and continuous automated measurements of the facial blood flow could be used to indicate when, and if, MTS occurs. As severe facial flushing in relation to MTS may be associated with postoperative complications [9], it would be advantageous to identify the presence of the syndrome already during the operation as countermeasures may be initiated. Laser speckle contrast imaging (LSCI) is a non-touch device that provides an estimate of tissue perfusion in the area of interest [10] and could, in theory, be applied to quantify facial flushing in relation to MTS.

This study aimed to determine facial skin blood flow by LSCI during MTS to quantify the subjectively determined flushing scores. We hypothesized that severe facial flushing would be related to the highest concentrations of plasma PGI_2 and accordingly to the highest levels of skin blood flow measured by LSCI.

2 Methods

This study was carried out between 2014 and 2016 and was approved by the Scientific-Ethical Committees, Capital Region, Denmark (No. H-3-2014-021) and registered at clinicaltrials.gov (ID: NCT02507414) before enrolment of patients.

Patients with upper gastrointestinal cancer scheduled for open surgery in the liver (resection of minimum two segments; group Liver), stomach (subtotal or total gastrectomy; group Gastrectomy), or pancreas (Whipple's procedure; group Whipple) were screened for eligibility and were consecutively enrolled. Patients included in other scientific studies, scheduled for robotic-assisted procedures, without informed consent, or under the age of 18 years were excluded. Written and oral instructions of the study protocol were provided at least 7 days before planned surgery and a verbal, as well as written consent, was obtained.

2.1 Anesthesia and hemodynamic monitoring

Patients were anesthetized according to a standardized regime with propofol and remifentanil while cisatracurium facilitated oral intubation. General anesthesia was maintained by continuous infusion of remifentanil and propofol,

and a thoracic epidural catheter was placed between the 7th and 9th thoracic intervertebral space by loss of resistance technique and intravascular placement was ruled out by lack of response to administration of lidocaine 2% + 50 μg adrenaline. Epidural analgesia was initiated by bolus injection of 4 mL bupivacaine 0.5% followed by infusion of bupivacaine 0.25% with morphine (50 μg mL^{-1}) at 4 mL h^{-1} at the start of the procedure.

Warmed lactated Ringer's solution was provided at approximately 3 mL kg^{-1} h^{-1} during surgery and optionally supplemented by 5% human albumin if considered indicated by the anesthesiologist. Blood loss was replaced with allogenic blood if hemoglobin dropped below 4.3 or 5.0 mmol L^{-1} if the patient was known with ischemic heart disease. If significant bleeding occurred platelets and fresh frozen plasma were administered together with packed red blood cells in a balanced way and guided by thromboelastography. At the discretion of the anesthesiologist, bolus injections and/or continuous infusions of vasopressors were administered aiming at a mean arterial pressure (MAP) > 60 mmHg. Ephedrine and/or phenylephrine were provided as bolus injections, and for continuous infusion, phenylephrine or norepinephrine was administered.

Patients in group Whipple or Liver were provided 125 mg i.v. methylprednisolone (Solumedrol®, Pfizer, NY, USA) at induction of anesthesia according to the department's treatment guideline.

Hemodynamic variables were continuously sampled during surgery using modified pulse contour analysis (Nexfin®, BMEYE B.V., Amsterdam, NL) via a catheter in the radial artery of the non-dominant arm and included heart rate (HR), stroke volume (SV), cardiac output (CO), systemic vascular resistance (SVR), and MAP.

2.2 Facial flushing

Facial flushing was evaluated according to Nomura et al. [1], adapted from Koyama et al. [11], where grade I involve either forehead or cheeks while grade II includes the whole face. During the first hour of surgery, the occurrence of flushing was noted and graded by the observers. The nurse anesthesiologist confirmed the assessment and any disagreement were settled by discussion in the team.

2.3 Laser speckle contrast imaging

Continuous measurements of facial blood flow on the cheeks and the forehead were carried out by LSCI (MoorFLPI, Moor Instruments Ltd., Axminster, UK). In short, laser speckles are formed when rough surfaces are illuminated by laser light leading to the occurrence of a scatter pattern. By use of a charge-coupled camera fluctuation of the speckle pattern can be analyzed as perfusion units (LSPU), which

are considered a measure of tissue perfusion [10, 12, 13]. LSCI can measure in real-time without tissue contact and may be regarded as a more accurate and objective method to estimate the grade of facial flushing.

The device was placed 25 cm perpendicular to the tissue surface and the first hour of surgery was recorded. Blood flow analyses were performed post-hoc, and regions of interest (ROI) covering an area of 1 cm^2 were defined as one cm above the glabella ("forehead") and as one cm medial to the cheekbone ("cheek") using MoorFLPI Review (Vs. 4.0, Moor Instruments Ltd.). Then, data extracted from the selected ROIs were acquired using a programmed algorithm (Python vs. 2.7.6, Python Software Foundation, Wilmington, DE, USA) and for each ROI a median value over a period of 30 s was chosen as previously described [10].

2.4 PGI$_2$ analysis

Due to the short half-life of plasma PGI$_2$ plasma 6-keto-PGF$_{1\alpha}$, a stable metabolite of PGI$_2$ was determined. Blood samples for the analyses were obtained at: **A** baseline (after induction of anesthesia) and after: **B** 15 min of surgery, **C** 60 min of surgery, and **D** 120 min of surgery. Arterial blood was collected in EDTA tubes (BD Vacutainer, 2×6 mL) and centrifuged at 3000 rpm min^{-1} for 10 min at 4 °C and plasma were stored in cryotubes (CryoPure 1.8 mL, Sarstedt, Nürnbrecht, DE) at −80 °C until analysis. Enzyme-linked immunosorbent assay (ELISA) kits from two manufacturers (Enzo Life Science, Lörrach, Germany, ADI-900-00 and Cayman Chemicals, Ann Arbor, MI, USA, 515211.96-CAY) were tested for eligibility for human EDTA plasma according to the manufacturers' instructions.

2.5 Statistics

The incidence of MTS is 30 to 85% [1] and using this assumption, a power calculation of the percentage difference between the two groups predicted that 15 patients were required in each group (power: 0.9, $\alpha = 0.05$). The study aimed at including 25 patients in each group to account for drop-outs.

Statistical analysis was by IBM SPSS (IBM SPSS Statistics for Windows, vs. 22.0. Armonk, NY, USA) and graphs were constructed by GraphPad Prism software (vs. 7, GraphPad Software Inc., CA, USA). Data were tested for normality using the Shapiro–Wilk test, and due to non-normal data distribution, non-parametric statistics were chosen. Patients were allocated into three groups according to the subjectively determined flushing grades (no flushing and grade I or II). Differences between the groups were tested by the Kruskal–Wallis *H*-test with Bonferroni correction for multiple comparisons or Mann Whitney's *U*-test if two groups were compared. To evaluate baseline characteristics the X^2-test or Fisher's exact test was applied for dichotomous variables, and a P-value ≤ 0.05 (two-sided) was considered statistically significant. Receiver operating curves (ROCs) were constructed for determination of a cut-off value including sensitivity and specificity for flushing grades evaluated by LSCI. Hemodynamic variables were calculated over a 30 s sampling period, and all data are presented as medians with interquartile range.

3 Results

75 patients were screened for eligibility of which 18 patients were excluded due to: missing data on the degree of flushing (n = 7) or LSCI file (n = 1), the intended intervention was changed (n = 1), or because the operation was discontinued due to disseminated disease verified after laparotomy (n = 9). Thus, 66 patients were included for analysis: Group Whipple (n = 21), group Liver (n = 23), and group Gastrectomy (n = 22). There were no significant differences in baseline characteristics between the groups (Table 1).

Table 1 Baseline characteristics

	All patients	Gastrectomy	Whipple	Liver	*P*-value
Age, years, median (IQR)	66 (57–71)	66 (55–73)	69 (63–73)	61 (54–68)	0.11
BMI, median (IQR)	25 (23–28)	23 (21–27)	26 (23–28)	26 (23–28)	0.39
Sex, male, n (%)	36 (55)	12 (55)	8 (38)	16 (70)	0.11
Tobacco, active and former use, n (%)	44 (67)	18 (82)	12 (57)	14 (61)	0.47
Alcohol, > 21 units per week, n (%)	9 (14)	5 (23)	3 (14)	1 (4)	0.20
ASA 1–2, n (%)	47 (71)	13 (59)	15 (71)	19 (83)	0.22
ASA 3–4, n (%)	19 (29)	9 (41)	6 (29)	4 (17)	0.22

Values are median [interquartile range (IQR)] or n (%)

BMI body mass index, *ASA*: American Society of Anaesthesiologists physical status classification

P-values by Kruskal Wallis *H*-test and the X^2-test or Fisher's exact test for continuous and dichotomous variables, respectively

Table 2 Facial flushing

Characteristic	Gastrectomy	Whipple	Liver
Flushing, yes/no (%)	16/22 (73)	8/21 (38)	11/23 (48)
No flushing, n (%)	6 (27)	13 (62)	12 (52)
Grade I, n (%)	8 (36)	4 (19)	7 (30)
Grade II, n (%)	8 (36)	4 (19)	4 (17)

Flushing scores determined within the first hour of surgery by subjective investigator assessments. Values are n (%)
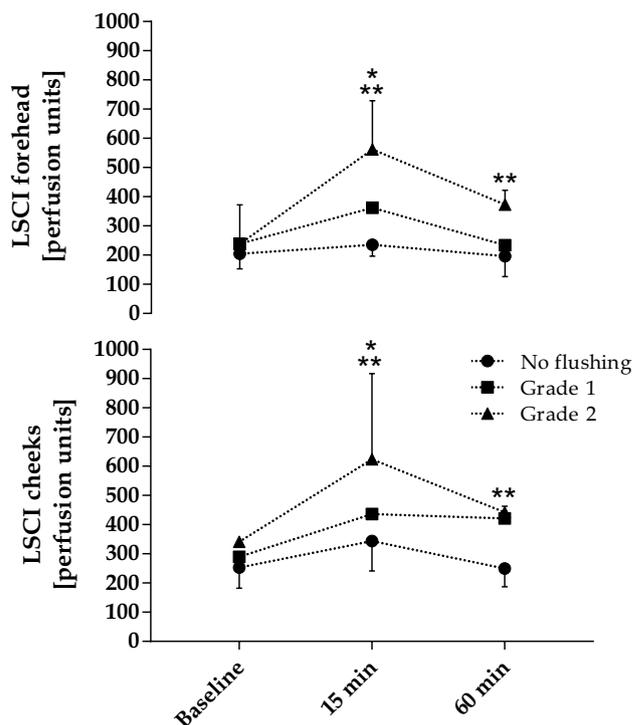
3.1 Facial flushing

Overall, facial flushing (grade I + II vs. none) was detected in 35/66 patients (53%) within the first hour of surgery. The highest frequency was found in group Gastrectomy (73%) compared with group Whipple (38%), and group Liver (48%). Grade I and II flushing accounted for 29% (n = 19) and 24% (n = 16) of all cases, respectively (Table 2). For patients administered preoperative methylprednisolone (group Liver and Whipple) the incidence of facial flushing was lower compared with patients receiving none (group Gastrectomy) (methylprednisolone: 19/44 (43%) vs. none: 16/22 (73%), P = 0.04).

3.2 LSCI

From baseline to 15 min of surgery, patients with grade II flushing demonstrated the highest blood flow in the forehead (238 [201–372] to 562 LSPU [433–729]) and the cheeks (341 [239–355] to 624 LSPU [468–917]), which were higher than for patients with grade I (forehead: 239 [177–298] to 362 LSPU [227–485], P = 0.04 and cheeks: 290 (220–368) to 436 LSPU [297–574], P = 0.04) or with no flushing (forehead: 204 [153–292] to 236 LSPU [196–375], P < 0.01 and cheeks: 253 [184–332] to 344 LSPU [241–414], P < 0.01 (Fig. 1)). Blood flow in the forehead and cheeks decreased by 60 min of surgery in the grade II flushing group but remained elevated (forehead: 373 LSPU [215–422] and cheeks 442 LSPU [323–463]) compared with patients with no flushing (forehead: 196 LSPU [126–262], P < 0.01 and cheeks: 250 LSPU [187–351], P = 0.04).

ROCs were constructed to determine a cut-off value for LSCI-assessed skin blood flow based on the subjectively determined flushing scores (Fig. 2). For grade II flushing vs. no flushing, a cut-off value by 425 LSPU (AUC 0.85 [0.75–0.95], P < 0.01) on the forehead was determined (sensitivity of 76% and specificity of 80%). Likewise, for grade II flushing, a cut-off value by 456 LSPU (AUC 0.85 [0.73–0.97], P < 0.01) on the cheeks was determined (sensitivity of 75% and specificity of 85%). No cut-off value between grade I vs. no flushing could be defined.

Fig. 1 Blood flow and facial flushing. Skin blood flows evaluated by laser speckle contrast imaging (LSCI) on the forehead and the cheeks according to the subjectively determined flushing scores. Values are medians with interquartile range. *P*-values by Kruskal Wallis *H*-test. *P < 0.05, different from grade I flushing; **P < 0.05, different from no flushing

3.3 Plasma 6-keto-PGF$_{1\alpha}$

Baseline plasma 6-keto-PGF$_{1\alpha}$ was not different between groups (P = 0.75) (Fig. 3). After 15 min of surgery, an increase was observed in patients with grade II flushing (476 [198–799] to 3309 pg mL^{-1} [1469–4946]), which was higher than for patients with no flushing (393 [144–690] to 968 pg mL^{-1} [732–1592], P < 0.01) but not different from patients with grade I flushing (459 [209–632] to 2239 pg mL^{-1} [1594–2614], P = 0.73). After 60 min of surgery, plasma 6-keto-PGI$_{1\alpha}$ normalized and no differences could be detected between groups (P = 0.12).

3.4 Hemodynamics

At baseline hemodynamic variables were not different between groups (Fig. 3). After 15 min of surgery, SVR decreased in patients with grade II flushing (1092 [904–1397] to 756 dyn s cm^{-5} [720–953]), which was lower than for patients with no flushing (1154 [910–1625] to 1138 dyn s cm^{-5} [901–1292], P = 0.01) but it only tended to be lower than for patients with grade I flushing (1236 [958–1529] to 997 dyn s cm^{-5} [762–1251], P = 0.10).
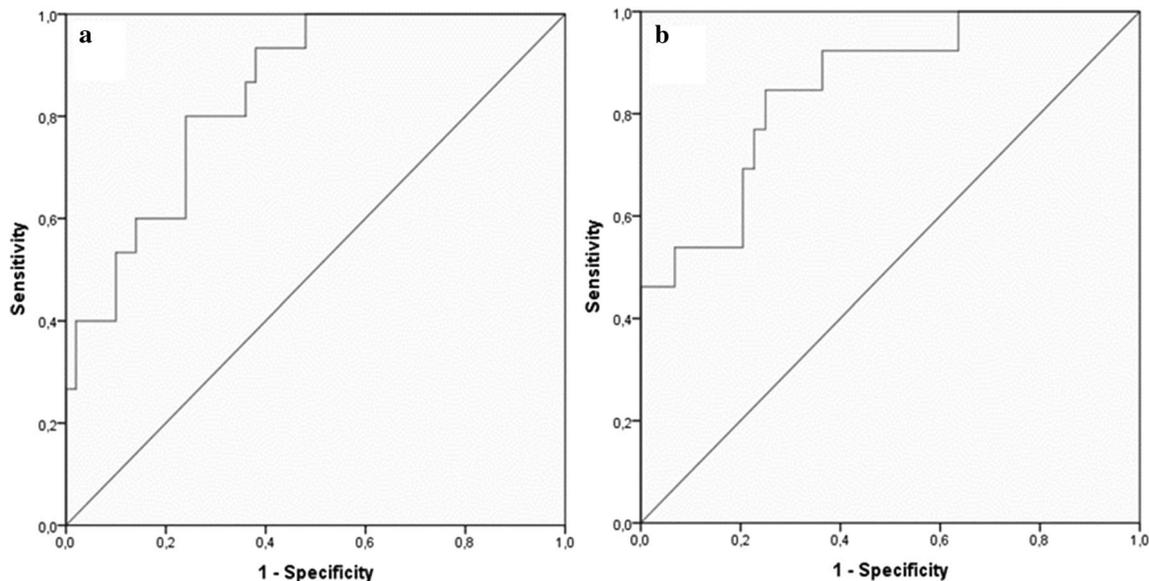
Fig. 2 Receiver operating curves. Determination of a cut-off value for blood flow evaluated by laser speckle contrast imaging based on grade II flushing vs. no flushing. **a** Forehead: 425 LSPU (AUC 0.85 [0.75–0.95], P < 0.01, sensitivity of 76% and specificity of 80%); **b** Cheek: 456 LSPU (AUC 0.85 [0.73–0.97], P < 0.01, sensitivity of 75% and specificity of 85%)

Accordingly to the reduction in SVR, CO increased (4.4 [3.5–5.4] to 6.0 L min^{-1} [4.7–6.7], P = 0.04) leaving MAP stable.

At 60 min, no significant differences in hemodynamic variables were found between groups, however, CO tended to be higher (5.1 L min^{-1} [4.3–6.1]) for patients with grade II flushing compared with patients with grade I (4.5 L min^{-1} [4.0–5.5], P = 0.06) or with no flushing (4.4 L min^{-1} [3.9–4.8], P = 0.06).

Vasopressor treatment provided as bolus injections or continuous infusions were not different between patients with flushing (G1 + G2) and no flushing during the first 30 min of surgery or the overall intraoperative period.

4 Discussion

To our knowledge, this is the first study to quantify the clinical appearance of MTS by a cut-off value determined by measuring skin blood flow on the forehead and the cheeks. Furthermore, we found that MTS is linked to a release of 6-keto-PGF$_{1\alpha}$ and systemic vasodilatation during major upper abdominal surgery. Thus, quantitative and qualitative verification of the MTS was demonstrated in patients undergoing either gastrectomy, Whipple's procedure or liver resection.

A clear difference in blood flow measured in the forehead and the cheeks were determined between grade II flushing and no flushing while grade I flushing could not be statistically distinguished from no-flushing. Accordingly, a cut-off

value for LSCI-assessed skin blood flow was defined for both the cheeks and the forehead for patients with grade II flushing vs. no flushing. The results indicate that LSCI can discriminate severe facial flushing from moderate and no-flushing, and thereby make the detection of MTS objective and automatic during surgery. By applying LSCI, certain inconsistencies concerning the subjective flushing scores may be obliterated as these are estimates based on investigator assessments including the severity and the extent of the flushing, i.e. flushing on either cheek, forehead, or both.

The pathophysiology of MTS is not fully understood, but PGI$_2$ is considered to be a key hormone in the systemic cardiovascular response [2, 3, 14–17]. We observed a noticeable increase in plasma 6-keto-PGF$_{1\alpha}$ in patients with grade I flushing (2239 pg mL^{-1}) and a higher plasma concentration for grade II (3309 pg mL^{-1}) after 15 min of surgery (Fig. 3). Likewise, patients with grade II flushing experienced a more severe vasodilatation (SVR: 756 dyn s cm^{-5}) compared with grade I (997 dyn s cm^{-5}) and no flushing (1138 dyn s cm^{-5}) illustrating the close inverse relationship between plasma PGI$_2$ and SVR.

Due to the systemic vasodilatation in response to MTS, a subsequent decrease in MAP is common. The hypotension is often to a moderate extent and recovers to normal values within 30 min of surgery [3, 16] but in some cases severe and prolonged hypotension is observed possibly dependent on the plasma concentration of PGI$_2$ [18, 19]. To restore MAP after MTS, endogenous compensatory mechanisms like sympathetic-mediated vasoconstriction and activation of the renin-angiotensin-aldosterone-system or administration
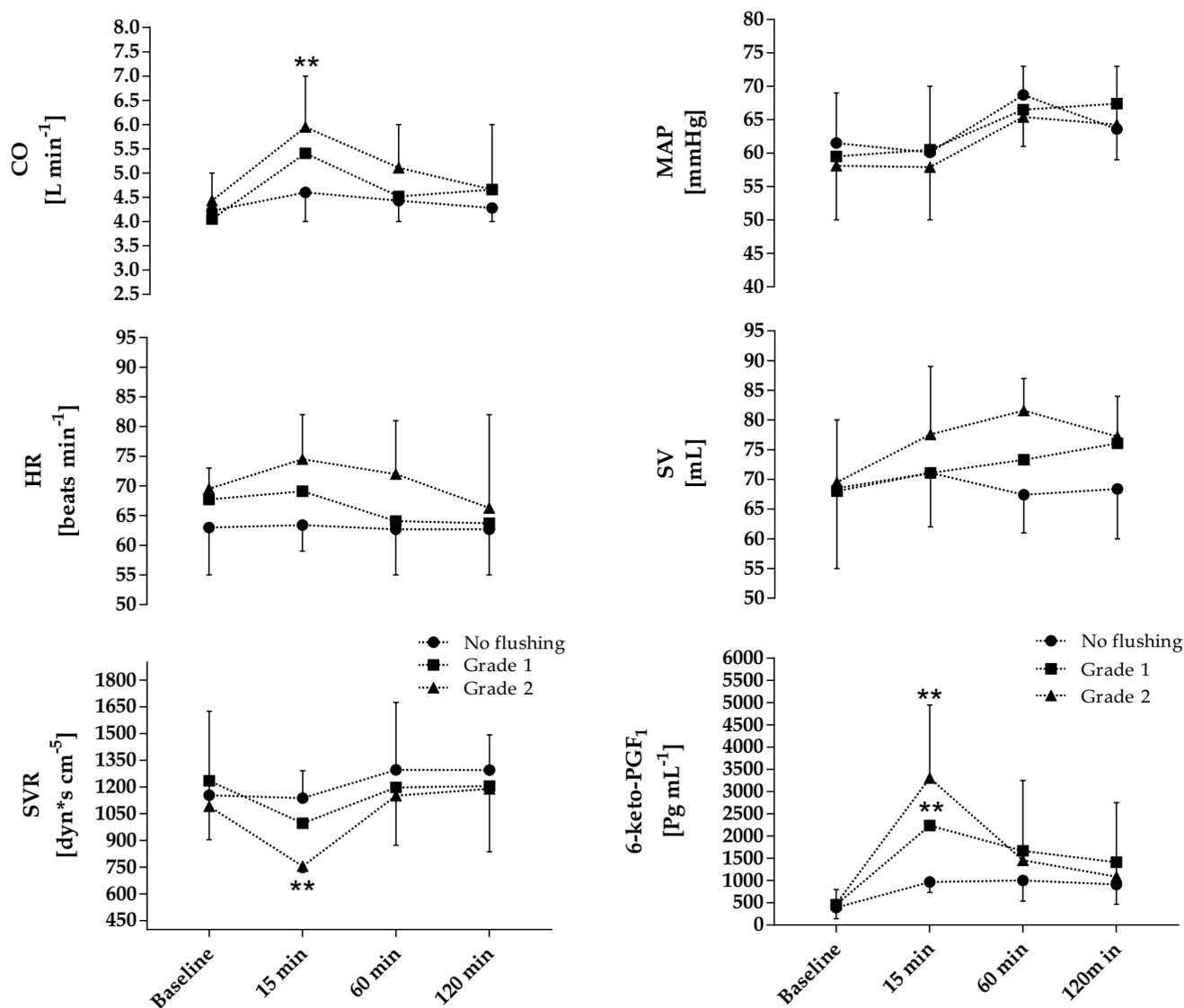
Fig. 3 Plasma 6-keto-PGF$_{1\alpha}$ and hemodynamic variables. Plasma 6-keto-PGF$_{1\alpha}$ and hemodynamic variables evaluated during surgery according to the flushing score. Values are medians with interquartile range. P-values by Kruskal Wallis *H*-test. *P < 0.05, different from grade I flushing; **P < 0.05, different from no flushing. *CO* cardiac output, *HR* heart rate, *SVR* systemic vascular resistance, *MAP* mean arterial pressure, *SV* stroke volume

of exogenous vasopressors seem essential. One study found an immediate increase in plasma epinephrine and arginine-vasopressin after intentional eventration and traction on the short bowel including an increase in plasma renin within 30 min after MTS, which was significantly higher than for patients treated with preoperative ibuprofen [3]. The direct or indirect vasoconstrictive effects of these hormones seem to contribute to hemodynamic stability after MTS, albeit additional exogenous treatment with vasopressors is often required to maintain MAP. In this study, the MAP was stable in both patients with and without flushing after 15 min of surgery, and surprisingly the administration of vasopressors was equal between the two groups of patients. This

discrepancy may be due to the inclusion of three types of surgical procedures where the choice of vasopressor was at the discretion of the responsible anesthesiologist. Thus, norepinephrine was primarily used for infusion during Whipple's procedure whereas phenylephrine was commonly administered during liver and gastric resections. Hence, the doses of vasopressors administered for patients with flushing vs. no flushing are difficult to calculate, and the results should be interpreted with caution, and we acknowledge this as a limitation of the study. Our findings are not supported by previous studies, as one study examined 50 patients undergoing esophagectomy, and it was reported that patients with grade II flushing required more doses of vasopressors

the first hour of surgery (ephedrine and/or phenylephrine) to maintain MAP > 60 mmHg [9]. These patients were more likely to develop severe postoperative complications (Dindo-Clavien score 3–5), i.e. complications requiring endoscopic, radiological, or surgical intervention and/or transfer to the ICU [20]. Taken together, MTS seems to increase the risk of intraoperative hypotension due to systemic vasodilation that, if not handled sufficiently by administration of fluid [21] and vasopressors [22], could lead to postoperative complications [22, 23]. To standardize the verification of MTS, we suggest that LSCI could provide an objective evaluation of the syndrome; at least to detect patients with grade II flushing as this group may be particularly susceptible to complications. We accept, however, that a broader database of outcomes related to MTS is warranted to isolate the syndrome as an independent risk factor.

Several studies have evaluated the effects of non-steroidal anti-inflammatory drugs (NSAID) administered to influence the development of MTS [2–4, 6, 14]. One study reported that preoperative administration of 400 mg i.v. Ibuprofen reduced plasma PGI_2 after traction of the small bowel and the hemodynamic variables were stable compared with the placebo group [3]. Likewise, i.v. Flurbiprofen administered after the onset of MTS reduced the extent of the systemic vasodilatation [6]. Thus, NSAIDs seems useful for attenuating MTS, although impairment of coagulation [24] and an increased risk of anastomotic dehiscence [25] are known side effects.

Interestingly, Brinkmann et al. reported that patients pre-treated with ibuprofen had a significantly higher arterial endotoxin concentration and gram-negative bacteria were isolated in mesenteric lymph nodes exclusively in NSAIDs pretreated patients [15]. The study concluded that the endogenous PGI_2 release during MTS might play a role in maintaining splanchnic microcirculation and preserving gut mucosal barrier function because PGI_2 may have a cytoprotective effect [15]. Yet, whether a higher plasma concentration of endotoxin is more counterproductive than the MTS is unknown.

In this study, a lower incidence of MTS was observed among patients receiving i.v. methylprednisolone at the induction of anesthesia (Whipple 38% and Liver 48% vs. Gastrectomy 73%). The effect of the drug could explain the lower incidence of MTS, albeit corticosteroids have primarily been reported to inhibit the systemic inflammatory response syndrome, and not MTS [26, 27]. In a recent trial, yet unpublished, we demonstrated that plasma interleukin-6 (IL-6) concentrations (an inflammatory cytokine associated with "surgical stress") were significantly elevated for patients with grade II flushing at the end of surgery. Given that prolonged and excessive levels of plasma IL-6 is associated with postoperative morbidity [28], we speculate that MTS could be linked to the initiation of an unfavorable

immunologic response. Accordingly, in addition to reducing the immunologic response to surgery, corticosteroids may also prove efficient for attenuating MTS. However, this association needs further attention.

The strengths of this study include the consecutive enrolment of patients. Despite the non-randomized study setup and the inclusion of patients undergoing various surgical procedures, the baseline characteristics were not significantly different between groups, thus, reducing the risk of selection bias. The subjective grading of facial flushing applied in the study may have under- or overestimated the incidence of MTS, but to minimize the potential variability, the final flushing score was settled by two persons.

5 Conclusion

This study found that MTS is linked to increased facial skin blood flow, to systemic vasodilation, and to a release of plasma 6-keto-$PGF_{1\alpha}$ during major upper abdominal surgery. By applying LSCI, we could quantitatively register and define a cut-off value for blood flow on the forehead and the cheeks, and thereby provide an objective tool for intraoperative verification of MTS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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