Pathophysiology 26 (2019) 115–120

Contents lists available at ScienceDirect

Pathophysiology

journal homepage: www.elsevier.com/locate/pathophys

The pathophysiology of complications after laparoscopic colorectal surgery: Role of baroreflex and chemoreflex impairment

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ARTICLE INFO

Article history:
Received 12 January 2019
Received in revised form 14 April 2019
Accepted 21 May 2019

Keywords:
Baroreflex
Pneumoperitoneum
Chemoreflex

ABSTRACT

Introduction: The aim of this study was to assess the dynamics of baroreflex sensitivity (BRS) during laparoscopic colorectal surgery in patients with different chemoreflex sensitivity assessed with breath-holding test.

Methods: The study included 80 patients (mean age, 68 ± 7 years) who underwent routine laparoscopic colorectal surgery under general/epidural anaesthesia. Patients were retrospectively divided into two groups: with normal (breath-holding duration ≥38 s, group N [n = 42]) or high (breath-holding duration <38 s, group H [n = 38]) chemoreflex sensitivity. BRS was initially evaluated after arterial catheter placement before induction, after induction, after pneumoperitoneum, after extubation, and 6 h and 24 h after extubation.

Results: Average BRS was significantly lower in the group with high peripheral chemoreflex sensitivity at all time points. The use of pneumoperitoneum did not significantly influence BRS in either group. After the surgery and 6 h after extubation, no significant changes were observed. After 6 h of the surgery, 11.9% of patients in group N and 57.8% of those in group H ($p < 0.05$) had severe baroreflex dysfunction (BRS < 3 ms/mmHg). After 24 h, only two patients in group N (vs 13 [34.2%] in group H, $p < 0.05$) had this dysfunction.

Conclusion: Patients with high chemoreflex sensitivity have lower BRS, and it decreases further after anaesthesia induction. The recovery process can take up to 24 h, with an increased risk of perioperative complications in patients with high preoperative chemoreflex sensitivity. The use of pneumoperitoneum does not significantly affect BRS.

1. Introduction

Despite the great attention given to improving the quality of anaesthesia in abdominal surgery, many complications pose problems, and some of these significantly affect treatment and can be life-threatening [1].

Among the specific complications of anaesthesia, acute disturbances of systemic haemodynamics, hypothermia, and metabolic disorders must be identified. The most common complication in abdominal surgery is arterial hypotension, which occurs in 50% or more cases [2]. The causes of haemodynamic disorders in abdominal surgery are diverse. First, the course of anaesthesia is determined by the patient's initial condition [3]. A large proportion of patients have some serious chronic diseases, and both the absence of concomitant disease therapy and the continuous intake of drugs significantly complicate the course of anaesthesia [4]. Hypotension in abdominal surgery disrupts organ perfusion and causes organ dysfunction, which in turn lead to complications. The stability of haemodynamics depends not so much on the presence or absence of chronic cardiac pathology, but rather on how much the functional reserves of the cardiorespiratory system are reduced, that is, how much it is able to withstand the factors affecting it that arise during anaesthesia.

Laparoscopic techniques are increasingly being introduced in abdominal surgery, and although these have considerable advantages, they also have significant drawbacks [5]. Haemodynamic changes in laparoscopy are the result of the combined effects of increased intra-abdominal pressure, pneumoperitoneum, and changes in the patient's position on the operating table. In addition, the pathophysiological changes can occur because of the increase

Abbreviations: ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; BHT, breath-holding test; BRS, baroreflex sensitivity; LVEF, left ventricle ejection fraction; ISBP, invasive systolic blood pressure.

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https://doi.org/10.1016/j.pathophys.2019.05.004
0928-4680/

in the tone of the vagus nerve and the occurrence of arrhythmias. Insufflation of gas into the abdominal cavity causes significant shifts in haemodynamics and disrupts abdominal organ perfusion.

The functionally integrated cardiorespiratory system is a mechanism responsible for adapting the organism to changes in the environment [6]. It is the first system that reacts to changes, thereby determining the state of the organism under certain conditions. The systemic level of control of the blood gases and arterial pressure is provided by the reflex regulation of this system, whose main elements are the chemoreflex and arterial baroreflex. The sensitivity of the chemoreflex is a parameter reflecting the degree of response of the respiratory system to the changes in blood gas composition; it is a marker of the disruption of reflex regulation of the cardiorespiratory system in the course of progression of chronic diseases [7,8]. Patients with high sensitivity of chemoreflex are known to be more prone to haemodynamic instability during general anaesthesia [9]. Disturbances in chemoreflex sensitivity lead to an increase in sympathoexcitation [10] and a decrease in arterial baroreflex sensitivity (BRS) [11], which is the cornerstone of maintaining blood pressure in response to its changes.

Therefore, the objective of this study was to assess the dynamics of arterial BRS during laparoscopic colorectal surgery in patients with different chemoreflex sensitivity evaluated with breath-holding test.

2. Material and methods

2.1. Study protocol

The study included 80 patients (mean age, 68 ± 7 years) who underwent routine laparoscopic colorectal surgery. The physical status of the patients corresponded to classes 2–3 of the ASA classification. The exclusion criteria were as follows: concomitant pulmonary diseases, history of thoracic surgery, significant systolic dysfunction (LVEF less than 40%), and body mass index more than 30 kg/m^2. Patients were retrospectively divided into two groups with normal (breath-holding duration $\geq$38 s, group N [n = 42]) or high (breath-holding duration <38 s, group H [n = 38]) chemoreflex sensitivity [12]. The level of chemoreflex sensitivity, as well as the value of arterial BRS, was assessed by a specialist who was neither involved in the surgery and anaesthesia management nor in the postoperative treatment, and did not influence the decision-making of the clinicians. Permission of the Ethics Committee was obtained for the study in February 2017; all participants signed an informed consent before inclusion to the investigation.

2.2. Anaesthesia and analgesia

After the patient was admitted to the operative room and a peripheral vein was cannulated, an epidural catheter was inserted at the thoracic level (Th8–Th10) before anaesthesia induction. A bolus of 5 mL of 0.5% bupivacaine was started as soon as the epidural catheter was in place, and a continuous perfusion of 0.2% ropivacaine at 6 mL/h was initiated until the end of the surgical procedure. Thereafter, an arterial catheter was inserted into a radial artery to start invasive blood monitoring. In both groups, anaesthesia induction was performed using propofol (1–2 mg/kg), fentanyl (2–3 μg/kg), and rocuronium (0.6 mg/kg) for muscle paralysis. After tracheal intubation, maintenance of anaesthesia was performed using sevoflurane in a mix of oxygen/fresh air (with a 40–60 BIS target) and boluses of rocuronium as needed according to the TOF-monitor. Analgesia was ensured using the ropivacaine solution. At the end of the surgery, infusion was continued in the intensive care unit to achieve a visual analogue scale score <4 with a bolus of 3 mL of the solution allowed every 40 min (patient-controlled epidural analgesia). During anaesthesia and for the following postoperative days, maintenance of mean blood pressure more than 70 mmHg and diuresis more than 0.5 mL/kg/h was aimed for, first by the administration of 500 mL saline solution. Norepinephrine at a rate of 0.01–0.2 μg/kg/h was used as a vasopressor if blood pressure was not corrected by saline administration.

2.3. Surgical techniques

Four experienced laparoscopic surgeons performed all the procedures. Mechanical bowel preparation was used for all sigmoid and rectal procedures. Cefazolin (2 g) and metronidazole (500 mg) were administered 30 min before anaesthesia induction. Anti-embolic stockings were applied before positioning the patients on the operating table, and unfractionated heparin (5000 U) was injected subcutaneously 12 h before surgery. Laparoscopy was achieved using a 12-mm untipped Hasson cannula inserted under direct vision into the peritoneal cavity through a small vertical infra-umbilical incision to establish the pneumoperitoneum, which was maintained with carbon dioxide insufflation to a pressure of 12 mmHg. This incision was later extended to 4–5 cm to deliver the colon or sigmoid for resection and re-anastomosis. Three additional 5-mm trocars were inserted under laparoscopic vision. For right and left colectomy, the colon was completely mobilized laparoscopically, and the blood vessels were divided intracorporeally. The resection and anastomosis were performed extracorporeally. For rectal resections, the anastomosis was completed extracorporeally through a 10-cm horizontal incision and by using the double-shaped end-to-end anastomotic circular stapling technique. Nasogastric tube and abdominal drains were not used.

2.4. Chemoreflex sensitivity

The breath-holding test was performed a day before surgery as follows [13]: voluntary breath-holding duration was assessed three times, with 10-min intervals of normal resting breathing. After inspiration of an atmospheric air volume equal to 2/3 of the vital lung capacity $\pm$ 15% (controlled with spirometry), the participants were asked to hold their breath, and the duration of voluntary apnoea was measured from the beginning of the voluntary inspiration until the reflex contractions of the diaphragm were felt by the researcher's palm. The mean value of the duration of three samples was calculated.

2.5. Baroreflex measurement

The injection method was used in all patients. Inter-beat interval responses to vasodilator-induced hypotension were used to measure BRS. Graded boluses of nitroglycerin (3 μg/kg) were injected via the right internal jugular vein [14]. Invasive systolic blood pressure (ISBP) for each beat and the corresponding RR interval with a one-beat delay were recorded using a record module (Nihon Kohden MU-651 K; Japan) until the ISBP decreased to the bottom-most level. BRS was defined as the change in RR interval in ms per mmHg change in ISBP. BRS values were calculated using the method described earlier [15], and the formula was BRS (ms/mmHg) = (RR interval before injection − RR interval after injection)/(ISBP before injection − minimal ISBP after injection). The level of BRS less than 3 ms/mmHg was accepted as a reduced BRS because it is well-known as an independent predictor of complications in patients with chronic heart failure [16]. Evaluation was performed at the following stages: initially after arterial catheter placement before induction (T1), 30 min after induction (T2), after pneumoperitoneum (T3), 30 min after extubation (T4), 6 h after extubation (T5), and 24 h after extubation (T6).

Table 1
Demographic and clinical characteristics of the study population.

Parameter	Group N	Group H	P value
Age, y	65 ± 7	63 ± 8	0.35
ASA class	2.4 ± 0.5	2.5 ± 0.4	0.34
BMI, kg/m^2	23.6 ± 2.3	22.1 ± 2.1	0.12
Breath-holding duration, s	45 ± 7	23 ± 6	<0.001
BRS, ms/mmHg	7.07 ± 1.44	4.54 ± 1.31	<0.001
Medical therapy			
ACE-I/ARB, n	18	24	0.12
ß-blockers, n	19	17	0.31
Aldosterone antagonists, n	9	12	0.36
Loop diuretics, n	3	5	0.41
Thiazide diuretics, n	3	6	0.74
Statins, n	45	48	0.49

2.6. Outcome registration

Failure to recover normally was defined using the Clavien–Dindo scale with a grade 2 or higher complication representing clinically important deviation from the planned post-operative period. This scale was assessed 48 h after extubation, a day after the last baroreflex measurement. The length of hospital stay was also registered.

2.7. Statistics

The sample size for this study was determined for the primary endpoint of Baroreflex sensitivity. Preliminary data for this end-point were available from a study that tested Baroreflex sensitivity in healthy subjects with different breath-holding duration. On the basis of the data from this previous study, it was determined that for the endpoint of Baroreflex sensitivity, a sample size of $n = 40$ patients per group would provide statistical power (two-tailed, $\alpha = 0.05$) of greater than 80% to detect a difference between the treatment groups of 1 ms/mmHg.

Data showed normal distribution (Kolmogorov–Smirnov test) and were thus presented as mean ± standard deviation. BRS measurements in each group in the different time points were compared using repeated-measures analysis of variance. Groups were also compared at each time point by using the two-sample *t*-test. Baseline patient and procedural characteristics and other outcomes were compared across the groups by using Fisher's exact test for categorical variables, and the two-sample *t*-test for continuous variables. In all cases, P-values <0.05 were considered statistically significant. To evaluate the prognostic value of breath-holding test in prediction of postoperative complication a logistic regression was used.

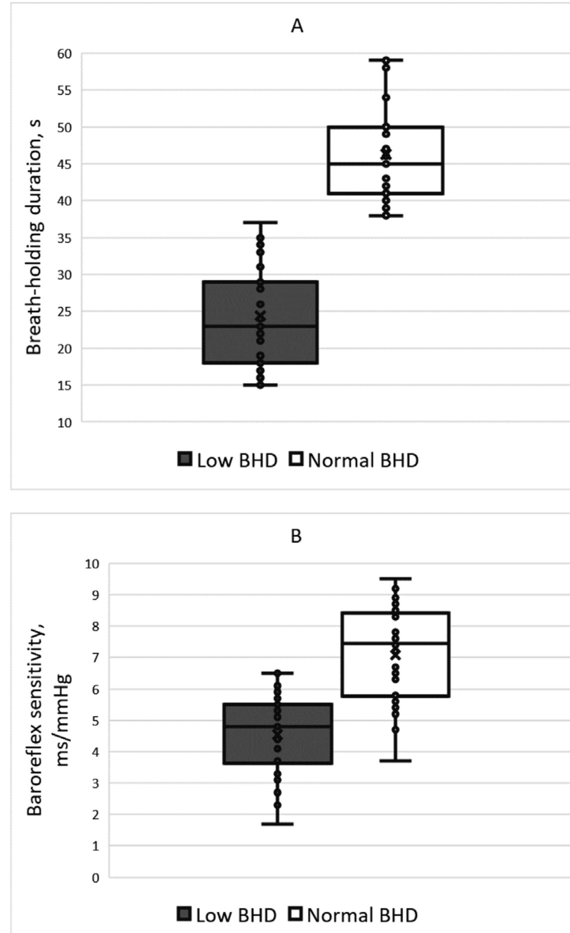
3. Results

Initial parameters of patients in both the groups are presented in Table 1. No significant differences were observed in sex, age, concomitant diseases, physical status, and medication use.

BMI, body mass index; BRS, baroreflex sensitivity; ACE-I/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker

The average breath-holding duration was 45 ± 7 s in group N and 23 ± 6 s in group H ($p < 0.001$), BRS was 7.07 ± 1.44 ms/mmHg and 4.54 ± 1.31 respectively ($p < 0.001$) (Picture 1).

The average BRS was significantly lower in group H, remaining lower at all stages of the study (Table 2). After anaesthesia induction, a trend of decreasing BRS was observed in both the groups. The use of pneumoperitoneum did not significantly influence BRS in either group. After the end of the surgery and 6 h after extubation, no significant changes were observed. BRS evaluation after 24 h showed that although BRS in both the groups were significantly higher than at previous time points, they did not return to the initial values.



Picture 1. Duration of breath-holding (A) and Baroreflex sensitivity (B) in groups with low (grey boxes) and normal (white boxes) breath-holding duration.
BHD – breath-holding duration.

Table 2
Dynamics of baroreflex sensitivity.

Study time point	Group N	Group H	P value between groups
(T1) Baseline, ms/mmHg	7.07 ± 1.44	4.54 ± 1.31	p < 0.001
(T2) After anaesthesia induction, ms/mmHg	4.91 ± 1.37*	2.76 ± 0.81*	p < 0.001
(T3) After pneumoperitoneum use, ms/mmHg	4.51 ± 1.36*	2.68 ± 0.72*	p < 0.001
(T4) End of surgery, ms/mmHg	4.23 ± 1.39*	2.98 ± 0.58*	p < 0.001
(T5) 6 h after extubation, ms/mmHg	4.30 ± 1.02*	3.02 ± 0.49*	p < 0.001
(T6) 24 h after extubation, ms/mmHg	5.98 ± 1.39*#	3.35 ± 0.57*#	p < 0.001

- $p < 0.001$ compared to T2, T3, T4, T5.
* Compared to baseline.

Despite the same dynamics in both the groups, after 6 h of surgery, 11.9% of patients in group N and 57.8% of those in group H ($p < 0.05$) had BRS values below 3 ms/mmHg, which was regarded as severe baroreflex dysfunction. After 24 h, only two patients in group N (vs 13 [34.2%] in group H, $p < 0.05$) showed this dysfunction.

Intraoperative characteristics, such as the duration of anaesthesia, blood loss, and blood product administration, were similar between the two study groups; however, patients in group

Table 3
Intraoperative and postoperative outcomes.

Parameter	Group N	Group H	P value
Duration of anaesthesia, min	145 ± 42	154 ± 56	0.23
Fluids administered, mL/kg/h	5.3 ± 1.2	7.3 ± 1.4	0.012
Need for vasopressors, n	17	27	0.043
Length of hospital stay, days	7.3 ± 2.4	9.2 ± 2.7	0.032
Clavien–Dindo grade ≥2, n	12	21	0.024

Table 4
Logistic regression model for prediction of postoperative complications.

Variable	Coefficient	Std. error	Odds ratio	95%CI	P
Age	0.11	0.05	1.1	1.0-1.3	0.04
Low BHD	2.10	0.68	8.2	2.1-31.4	<0.001
ASA class	2.88	0.71	17.9	4.5-71.5	<0.001
Constant	−16.33				

BHD – breath-holding duration.

H required a higher frequency of support with vasopressors and a larger volume of administration of fluids for haemodynamic stability (Table 3). Patients with initially high peripheral chemoreflex sensitivity experienced more episodes of significant (Clavien–Dindo grade ≥2) morbidity by postoperative day 2. Prolonged hospital stay was also more likely in patients with initially high peripheral chemoreflex sensitivity.

Logistic regression was performed to assess the prognostic significance of the breath-holding test in prediction of postoperative complications (Clavien–Dindo grade ≥2). The analysis showed that the predictors of postoperative complications were the duration of BHT less than 38 s, advanced age, and higher ASA class ($\chi 2 = 33.9$, <0.001) (Table 4). Area under the ROC curve for the model was 0.85 (95%CI, 0.75-0.91).

4. Discussion

The main finding of our study is that arterial BRS decreases during anaesthesia, and its recovery to the baseline occurs on the second day of postoperative period. Pneumoperitoneum does not significantly affect the level of arterial BRS.

Initially, the level of arterial BRS was lower in the group of patients with high peripheral chemoreflex sensitivity, which was not surprising. Studies have shown that the progression of cardiovascular disease leads to the activation of peripheral chemoreceptors and an increase in sympathoexcitation, which is a characteristic vicious circle for many chronic diseases [17,18]. Moreover, these changes are the cause of the impairment in baroreflex control of the cardiovascular system. Therefore, Ponikowski showed that reduced arterial BRS is inversely correlated with peripheral chemoreflex sensitivity in patients with chronic heart failure [11], and this pattern does not change when treating patients with drugs affecting the renin-angiotensin system [19].

Anaesthesia induction led to a decrease in arterial BRS in both groups; however, the absolute value of BRS was lower in the group with initially high chemoreflex sensitivity. The obtained dynamics correlated with the results of earlier studies, which showed a decrease in baroreflex function during propofol anaesthesia [20,21]. Sellgren *J.* and Ejnell H. demonstrated that propofol is a potent inhibitor of sympathetic neuronal activity and decreases the sensitivity of the Baroreflex [22]. Another study found that the sensitivity of the baroreceptors was depressed by propofol infusion during general anaesthesia and lasted for up to 60 min after the discontinuation of propofol infusion in 13 healthy human volunteers [23]. Endotracheal intubation is known to be a sympathetic stimulus, and hence, it should be expected to increase blood pressure and BRS. However, patients with impaired cardiorespiratory regulation showed an opposite trend of a further decrease in blood pressure. The larger drop in blood pressure associated with a lower BRS in group H is consistent with this pathological condition, which is known to be affected by an altered sympathetic outflow to the vasculature in patients with impaired reflex regulation. In addition, increased peripheral chemoreflex is often associated with high sympathetic activity, and this condition may affect the centrally mediated control of blood pressure [11,24]. The abovementioned decrease in BRS was maintained throughout anaesthesia, which caused haemodynamic instability that was more pronounced in group H. This is confirmed by the requirement for a larger volume of infusion and a greater frequency of vasopressor use in group H than in group N.

The use of pneumoperitoneum did not significantly affect the dynamics of the baroreflex in either group. The influence of pneumoperitoneum on arterial BRS has not yet been well studied. Studies are more often limited to assessing the function of the autonomic nervous system. Thus, the authors of several studies noted an increase in the activity of the sympathetic nervous system [25,26], which may be caused by a decrease in cardiac output [27], hypercapnia [26,28], as well as stretching of the abdominal wall. Under these conditions, the aortic baroreceptors and carotid sinuses are under the influence of many factors that are difficult to take into account. F Raimondi et al. [29] demonstrated that the steep Trendelenburg position during general anaesthesia increases vagal outflow and the augmentation is similar to that observed in healthy awake men; moreover, the application of pneumoperitoneum after the steep Trendelenburg position does not evoke any additional cardiovascular autonomic response. Our study showed that pneumoperitoneum with a pressure of not more than 12 mmHg does not significantly affect BRS. However, this issue requires further investigation, especially when changing the body position (Trendelenburg and anti-Trendelenburg positions).

As already mentioned, the decrease in BRS remained throughout anaesthesia, but the baroreflex function was not restored immediately after the restoration of consciousness. This correlates with the data of A. Toner, N. Jenkins, G. L. Ackland et al [30], who showed in their study that BRS remained below normal values even 6 h after the end of anaesthesia in patients with low initial values. Our data showed that some patients, especially those with initially high peripheral chemoreflex sensitivity, require more than a day for the restoration of the initial values. Long-term existing baroreflex dysfunction may cause an increase in the frequency of complications, particularly haemodynamic complications, in group H. The impairment of the baroreflex function may occur in afferent neurons transmitting information from the baroreceptors, brainstem neurons, or parasympathetic effect limb [31]. Experiments using laboratory models have demonstrated that the loss of vagal parasympathetic activity results in systemic inflammation in several organs, through the immuno-neuromodulation of nicotinic receptors on tissue-resident macrophages [32]. Furthermore, vagal denervation promotes persistent inflammation through the failure to regulate the resolution of inflammation [33]. The triad of inflammation, oxidative stress, and impaired BRS is well recognized in the development of chronic cardiometabolic disease [34]. In conscious rats, baroreflex loss of function impedes the attenuation of peripheral inflammation, mediated by the sympathetic neural drive [35]. Thus, acute inflammation together with a lack of established baroreflex 'reserve' may further detrimentally impair the neural anti-inflammatory armamentarium, which consequently jeopardizes metabolic homeostasis [36]. These changes result in a functional predisposition to postoperative complications. Considering the fact that disorders of baroreflex function in patients with initially low values persist for several days after surgery, the risk of complications is high.

Our study has some limitations. The duration of the voluntary breath-holding depends on several factors that were not taken into account in our study. Although peripheral chemoreceptors are included in the first line, and central chemoreception is a minor determinant of breath-holding duration [37], it is impossible to exclude the contribution of central chemoreceptors, especially with prolonged apnea. Also the duration of breath-holding depends on the metabolic rate, the initial blood gases [38], which were not taken into account in our study, although the influence of these factors, we believe, was minimized. It should be noted that the influence of these factors is also significant when using more valid methods. Undoubtedly, a large contribution to the duration is made by the initial volume of the lungs at the peak of inspiration [39], the objectification of this volume makes it more accurate and reproducible. BHT is not a direct method of chemoreflex sensitivity evaluation of, however, the presence of a strong relationship between the duration of breath-holding and the sensitivity of chemoreceptors allows a quick assessment of the function of the cardiorespiratory reflexes.

We evaluated only the sensitivity of baroreflex in response to pressure reduction after the injection of nitroglycerin and did not use a phenylephrine test. Given that hypotension is more frequent and more dangerous event in terms of complications, our main task was to assess the violation of the ability to respond to hypotension as the main mechanism to prevent complications. However, the study of another component of baroreflex is also of interest and requires further study.

5. Conclusion

Patients with high peripheral chemoreflex sensitivity have low BRS, and it decreases further after anaesthesia induction. Moreover, the recovery process can take up to 24 h after surgery. Perioperative baroreceptor dysfunction increases the risk of haemodynamic impairment during anaesthesia and the risk of postoperative complications in patients with preoperatively high chemoreflex sensitivity. The use of pneumoperitoneum does not significantly affect arterial BRS.

Authors' contributions

NT developed the concept and design of the study, the procedure for obtaining the data, performed an analysis and interpretation of data, participated in drafting the manuscript. IZ participated in the design of the study and performed the statistical analysis, was involved in drafting the manuscript, gave a final approval of the version to be published. Both authors read and approved the final manuscript.

Funding

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

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request

Ethics approval and consent to participate

Permission of the Ethics Committee was obtained for the study in February 2017; all participants signed an informed consent before inclusion to the investigation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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