Review Article

Perioperative goal directed therapy—current view

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Abstract: High-risk surgery is frequently associated with increased number of complications and higher mortality. Cardiovascular reserves of patients undergoing such procedures are frequently low, limiting their ability to sustain adequate organ perfusion. This puts the organs into the risk of hypoperfusion with loss of function and even failure. Perioperative goal directed therapy is can improve postoperative outcome of intermediate-to-high-risk surgical patients. Based on current evidence it seems to be associated with decreased postoperative length of stay, number of complications and possibly even mortality. In following narrative review, we discuss the contribution of perioperative goal directed therapy as well as its limits and possible future perspectives.

Keywords: Perioperative care; hemodynamics; fluid therapy

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Introduction

Cardiovascular (CV) morbidity and mortality is one of the major health-care problems. Almost 18 million patients die annually related to CV disease (1). Though our ability to treat CV diseases has improved significantly over the last decades, the prevalence of patients with decreased CV reserve is increasing (1). Besides, 313 million patients undergo surgery annually all over the world and 4.2 million presumably die within 30 days after surgery (2). It has been demonstrated previously, that these deaths frequently occur in small proportion (circa 10%) of high-risk patients (often with CV limitations) (3,4). These patients also consume much higher proportion of the global budget of perioperative care (5). Costs attributed to social care associated with decreased quality of life remain unresolved, but are presumably even higher.

The major driver of unfavorable postoperative outcome seems to be the patient's low functional reserve (6). The perioperative goal directed therapy (pGDT) was designed to optimize patients' CV performance and thus lower the risk of major complications in the perioperative period. Currently, this approach encompasses number of possible targets and/or treatment algorithms, which has been associated with decreased postoperative complications and improved outcome based on several large meta-analyses (7-11).

Historical perspective and physiological rationale

In 1988, Shoemaker *et al.* published seminal paper in which they described the concept of oxygen debt and its relevance for postsurgical period and development of complications (12). According to these data, surgical trauma and following period of healing are coupled with increased tissue oxygen consumption. This normally leads to increase of cardiac output and modulation of systemic vascular resistance in order to increase tissue oxygen supply. Patients able to cope

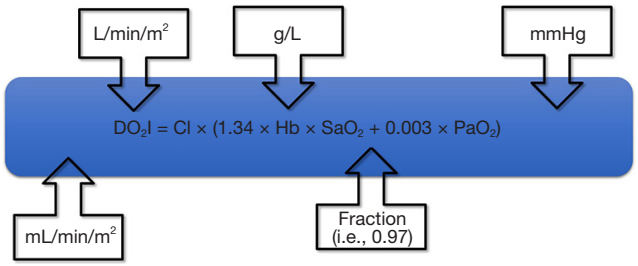

Figure 1 The oxygen delivery equation with relevant units. CI, cardiac index; DO_2I, index of oxygen delivery; Hb, hemoglobin concentration; PaO_2, arterial oxygen tension; SaO_2, hemoglobin oxygen saturation in arterial blood.

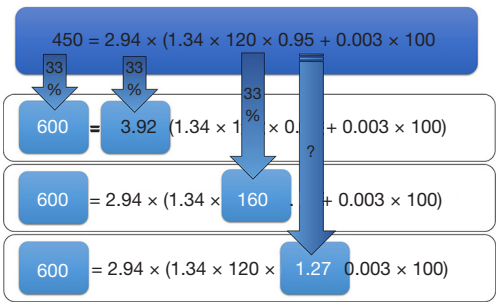

Figure 2 Numerical display of necessary change in individual parameters to reach supranormal oxygen delivery. Interpretation in the text.

with these increased demands usually pass the perioperative period without organ failure (13). Median of cardiac index (CI) observed by Shoemaker *et al.* was 4.5 L/min/m^2 (coupled with oxygen delivery of 600 mL/min/m^2 and oxygen consumption of 170 mL/min/m^2). In next prospective interventional study, Shoemaker *et al.* have demonstrated that iatrogenic increase of hemodynamic parameters to reach these predefined goals improved postoperative outcome in high risk surgical patients (12). In following decades, several other studies have evaluated this approach in various settings (14-18). Trials aimed on hemodynamic optimization of patients in intensive care have systematically failed to demonstrate any benefit (16-18). The reason for this has been attributed to the fact that dead tissue does not need the oxygen (19). The preemptive use in high-risk surgical patients seems to be the cornerstone of pGDT.

To understand the concept of pGDT one has to study the tissue perfusion physiology in detail. Because no stores of oxygen are available at the cellular level, the tissue is supplied on a continuous basis. In order to keep the adequate oxygen supply to tissues either its content in blood or the blood flow has to be modulated or organ demands has to be lowered. However, any change on global (macrocirculatory) level does not necessarily translate into the local/tissue (microcirculatory) level.

Blood supply to various organs is autoregulated to keep the constant blood flow under wide range of blood pressure, but outside these borders the local flow is dependent on systemic blood pressure. Hence, severe systemic hypotension or global hypoperfusion lead also to tissue hypoperfusion. Even more important is the redistribution of blood flow to "vital" organs (i.e., heart and brain). To maintain flow in vital organs the body decreases flow to "less important" tissues in case of severe hypoperfusion—therefore gastrointestinal tract, kidneys, skin, etc. may suffer undetected malperfusion (so called occult hypoperfusion). In 2004, Meregalli *et al.* have demonstrated, that signs of occult hypoperfusion (in this case increased serum lactate level) in spite of normal macrocirculatory parameters (normal blood pressure, etc.) were associated with unfavorable postsurgical outcome (20).

However, not all the determinants of the oxygen delivery equation (*Figure 1*) are clinically equal. If we presume a clinical case of a patient after surgical procedure having an oxygen delivery index of 450 mL/min/m^2, in whom we would like to increase it to 600 mL/min/m^2 (*Figure 2*). A change in CI of 33% (means absolute increase of 1 L/min/m^2) is usually affordable without problems. In contrary, the equal increase caused by elevation of the hemoglobin concentration would be hardly clinically acceptable, because the only way to modulate hemoglobin concentration perioperatively is coupled with transfusion of allogenic blood. Thus, the benefit of hemoglobin increase is largely limited by the risks of transfusion related complications. Moreover, according to current standards and guidelines the hemoglobin level ranging 7.0–1.0 g/L is taken as a sufficient (21).

Because of normally high oxygen saturation, desired increase is not affordable by oxygen therapy. An increase in oxygen saturation from 95% to 100% would be a mere 5% increase of oxygen delivery without further possibility to increase it under normobaric conditions. Therefore, modulating CI remains the cornerstone of pGDT. As previously stated in the concept of the functional hemodynamic monitoring (22), this is possible by modulating any of the three parameters affecting stroke volume (SV)—preload, contractility or afterload. This approach usually works quite well, but still there are some limitations. For instance, increasing the preload using

Table 1 Summary of the major positive outcomes of pGDT based on the meta-analysis by Chong *et al*. (7) and studies listed in *Table 2* (mortality only)

Parameter	Number of studies [subjects]	GRADE of evidence	Relative effect	Number needed to treat
Hospital LOS	62 [8,797]	Very low	−0.90 (0.48–1.32) days	N/A
Wound infection	32 [3,593]	Low	0.48 (0.37–0.63)	19
AKI	37 [4,310]	Low	0.73 (0.58–0.92)	29
Pneumonia	29 [2,776]	Low	0.69 (0.52–0.92)	38
Mortality [Chong *et al*. (7)]	52 [5,550]	Low	0.66 (0.50–0.87)	59
Mortality (*Table 2*)	94 [12,113]	N/A	0.80 (0.71–0.90)	56

pGDT, perioperative goal directed therapy; AKI, acute kidney injury; GRADE, Grades of Recommendation Assessment, Development and Evaluation; LOS, length of stay; N/A, not available.

fluids works only in patients operating on the steep portion of Frank-Starling curve, which is the majority of surgical patients. Inotropes (dobutamine or dopexamine) do increase heart contractility (and/or chronotropy), but for a price of increased myocardial oxygen consumption. Finally, afterload is usually modulated to reach adequate perfusion pressures, but this may be on the price of regional flow redistribution. Moreover, improving macrocirculatory variables need not directly link to improved microcirculation (so called micro-macro incoherence) (23). Disturbances in the microcirculation (capillary density, perfusion heterogeneity, etc.) may significantly impair the availability of substrates at the cellular level. In fully developed shock states (for instance in sepsis) this phenomenon may limit tissue perfusion and cellular metabolism even under normal systemic circulatory conditions. Red cell transfusion may impair microcirculation and blood rheology and fluids may contribute to edema formation and prolongation of diffusion distance.

Summary of available evidence

Over the last four decades starting with Shoemaker the concept of pGDT evolved in terms of monitoring devices used, populations studied and treatment goals reached. Several meta-analyses on this subject has been published over the last 10 years (7-9,11,24). In the two most recent ones the authors were able to identify 95 (7) and 112 (8) randomized controlled studies. Based on the meta-analysis by Chong *et al.* (7), the pGDT was associated with decreased mortality, morbidity and hospital length of stay (see *Table 1*). A major problem of such meta-analytical work is the great heterogeneity among included trials inducing a risk of bias. Therefore, authors of the last review (8) decided not to perform any kind of meta-analysis.

However, even these heterogeneous results may allow us to draw some conclusions. Based on our long-term screening of literature supported by results of multiple databases searches [i.e., for the purpose of previous meta-analysis (9)] our group is aware of 118 pGDT randomized prospective studies in human subjects published on this topic so far (as for May 2019) (*Table 2*).

Evolution of monitoring technologies

Naturally, the story began with pulmonary artery catheterisation (PAC): altogether 19 randomized controlled trials (RCTs) (accounting for 3,706 patients) have been published on pGDT driven by PAC so far [the study by Yassen in 2012 (132) is currently the last one]. PAC has many disadvantages for the pGDT protocols—first, it is highly invasive with high risk of complications. Besides, the pulmonary artery occlusion pressure (PAOP) is not a reliable predictor of fluid responsiveness (140). Contrary, PAC has always been recognized as the gold standard of CI monitoring. Nevertheless, based on our current knowledge the PAC is nowadays replaceable by less invasive devices and will have probably only minor impact on the future pGDT.

Transpulmonary dilution devices (PiCCO, VolumeView, LiDCO Plus) replaced the PAC monitoring because of their acceptable reliability and much easier applicability in many indications (especially for the critically ill). However, for the pGDT these devices never played a major role: mostly because the need of cannulation of central vein and major artery (mostly femoral), time-consuming calibration and costs. Only seven studies have been published using transpulmonary dilution techniques, and it seems the volumetric indices (unique for this kind of monitoring)

Table 2 Summary of available randomized controlled trials on the topic of pGDT

Author	Year	Device	Timing	Target variable	Type	Total number of patients	Mortality pGDT	Number of patients in pGDT arm	Mortality controls	Number of controls
Ackland (25)	2015	LiDCO	Post	SVmax	High risk	187	5.3%	95	5.4%	92
Bahlmann (26)	2019	FloTrac	Intra	SVmax	Thoracic	59	0.0%	30	0.0%	29
Bartha (27)	2013	LiDCO	Pre/intra	DO_2	Orthopaedic	149	4.1%	74	5.3%	75
Bender (28)	1997	PAC	Pre/intra/post	CI	Vascular	104	2.0%	51	1.9%	53
Benes (29)	2010	FloTrac	Intra	SVV	Abdominal	120	1.7%	60	1.7%	60
Benes (30)	2015	CNAP	Intra	PPV	Orthopaedic	80	2.5%	40	0.0%	40
Berlauk (15)	1991	PAC	Pre/intra	CI	Vascular	66	2.2%	45	9.5%	21
Bisgaard (31)	2013	LiDCO	Intra/post	SVmax	Vascular	64	3.1%	32	0.0%	32
Bisgaard (32)	2013	LiDCO	Intra/post	SVmax	Vascular	40	0.0%	20	0.0%	20
Bishop (33)	1995	PAC	Pre/intra/post	CI	Trauma	115	18.0%	50	36.9%	65
Bonazzi (34)	2002	PAC	Pre/intra/post	CI	Vascular	100	0.0%	50	0.0%	50
Boyd (35)	1993	PAC	Pre/intra/post	DO_2	High risk	107	5.7%	53	22.2%	54
Brandstrup (36)	2012	ODM	Intra	SVV	Abdominal	150	1.4%	71	1.3%	79
Broch (37)	2016	Nexfin	Intra/post	PPV	Abdominal	79	N/A	39	N/A	40
Buettner (38)	2008	PiCCO	Intra	SPV	High risk	80	0.0%	40	2.5%	40
Bundgaard (39)	2013	ODM	Intra	SVmax	Abdominal	42	N/A	21	N/A	21
Calvo-Vecino (40)	2018	ODM	Intra	SVmax	Abdominal	420	4.8%	209	4.3%	211
Cecconi (41)	2011	FloTrac	Intra	SVV	Orthopaedic	40	0.0%	20	0.0%	20
Colantonio (42)	2015	FloTrac	Intra	CI	Abdominal	80	0.0%	38	9.5%	42
Conway (43)	2002	ODM	Intra	FTc	Abdominal	57	0.0%	28	3.4%	29
Correa-Gallego (44)	2015	FloTrac	Intra	SVV	Liver	135	0.0%	69	3.0%	66
Demirel (45)	2018	Masimo/PVI	Intra	PVI	Abdominal	60	N/A	30	N/A	30
Donati (46)	2007	CVL	Intra/post	O_2ER	Abdominal	135	2.9%	68	3.0%	67
El Sharkawy (47)	2013	ODM	Intra/post	FTc	Liver	59	0.0%	29	0.0%	30
Elgendy (48)	2017	FloTrac	Intra/post	SVV	Abdominal	86	11.6%	43	7.0%	43
Fellahi (49)	2015	ECOM	Intra	SVV	Cardiothoracic	92	2.1%	48	4.5%	44
Figus (50)	2013	ODM	Intra	SVmax	Plastic	104	N/A	51	N/A	53
Fleming (51)	1992	PAC	Pre/intra/post	CI	Trauma	67	24.2%	33	44.1%	34
Forget (52)	2010	Masimo/PVI	Intra	PVI	Abdominal	82	4.9%	41	0.0%	41
Funk (53)	2015	FloTrac	Intra	SVV	Vascular	40	0.0%	20	10.0%	20
Funk (54)	2015	FloTrac	Intra/post	SVV	Plastic	20	N/A	10	N/A	10
Gan (55)	2002	ODM	Intra	FTc	High risk	100	N/A	50	N/A	50
Goepfert (56)	2007	PiCCO	Intra/post	GEDVI	Cardiothoracic	79	0.0%	39	0.0%	40
Goepfert (57)	2013	PiCCO	Intra/post	SVV	Cardiothoracic	100	0.0%	50	0.0%	50

Table 2 *(continued)*

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Author	Year	Device	Timing	Target variable	Type	Total number of patients	Mortality pGDT	Number of patients in pGDT arm	Mortality controls	Number of controls
Gómez-Izquierdo (58)	2017	ODM	Intra	SVmax	Abdominal	108	0.0%	54	0.0%	54
Hand (59)	2016	FloTrac	Intra	MAP	Plastic	94	N/A	47	N/A	47
Harten (60)	2008	LiDCO	Intra	PPV	Abdominal	29	7.1%	14	13.3%	15
Hasanin (61)	2019	Impedance	Intra	SVV	Abdominal	120	N/A	60	N/A	60
Challand (62)	2012	ODM	Intra	SVV	Abdominal	179	5.6%	89	4.4%	90
Chytra (63)	2007	OD	Post	SVmax	Trauma	162	16.3%	80	22.0%	82
Jain (64)	2012	LiDCO	Intra	SVV	Plastic	30	N/A	15	N/A	15
Jammer (65)	2010	CVL	Intra	$ScVO_2$	Abdominal	241	0.0%	121	0.0%	120
Jhanji (66)	2010	LiDCO	Post	SVV	Abdominal	135	10.0%	90	13.3%	45
Jones (67)	2013	LiDCO	Post	SVmax	Liver	91	2.2%	46	2.2%	45
Joosten (68)	2019	ClearSight	Intra	Closed-Loop	Abdominal	39	N/A	20	N/A	19
Kapoor (69)	2008	FloTrac	Intra	SVV	Cardiothoracic	27	0.0%	13	0.0%	14
Kapoor (70)	2016	FloTrac	Post	CI	Cardiothoracic	120	3.3%	60	10.0%	60
Kapoor (71)	2017	FloTrac	Intra/post	$ScVO_2$	Cardiothoracic	142	9.1%	66	15.8%	76
Kaufmann (72)	2017	ODM	Intra	SVV	Thoracic	96	N/A	48	N/A	48
Kim (73)	2018	FloTrac	Intra	SVV	Plastic	62	0.0%	31	0.0%	31
Kumar (74)	2015	FloTrac	Intra	CI	High risk	40	0.0%	20	0.0%	20
Kumar (75)	2016	FloTrac	Intra	SVV	Abdominal	60	N/A	30	N/A	30
Lai (76)	2015	LiDCO	Intra	SVV	Abdominal	220	2.8%	109	2.7%	111
Lee (77)	2015	NICOM	Intra	SVmax	Cardiothoracic	58	0.0%	29	0.0%	29
Lenkin (78)	2012	PAC/PiCCO	Intra	PAOP	Cardiothoracic	40	0.0%	20	0.0%	20
Li (79)	2017	FloTrac	Intra	VCCI	Not specified	232	N/A	116	N/A	116
Liang (80)	2017	FloTrac	Intra	SVV	Other	60	0.0%	30	0.0%	30
Liu (81)	2018	FloTrac	Intra/post	CI	Other	76	N/A	38	N/A	38
Lobo (82)	2000	PAC	Intra/post	DO_2	High risk	37	15.8%	19	50.0%	18
Lobo (83)	2006	PAC	Intra/post	DO_2	High risk	50	8.0%	25	28.0%	25
Lopes (84)	2007	IBPPlus	Intra	PPV	High risk	33	11.8%	17	31.3%	16
Luo (85)	2017	FloTrac	Intra	SVV	Neuro	145	5.5%	73	12.5%	72
Mayer (86)	2010	FloTrac	Intra	CI	Abdominal	60	6.7%	30	6.7%	30
McKendry (87)	2004	ODM	Post	SVmax	Cardiothoracic	174	4.7%	85	2.2%	89
McKenny (88)	2013	ODM	Intra	SVmax	Abdominal	101	0.0%	51	0.0%	50
Mikor (89)	2015	CeVOX	Intra	$ScVO_2$	Abdominal	79	2.6%	38	19.5%	41
Moppett (90)	2015	LiDCO	Intra	SVmax	Orthopaedic	114	15.7%	51	23.8%	63

Table 2 *(continued)*

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Author	Year	Device	Timing	Target variable	Type	Total number of patients	Mortality pGDT	Number of patients in pGDT arm	Mortality controls	Number of controls
Mythen (91)	1995	ODM	Intra	SVmax	Cardiothoracic	60	3.3%	30	0.0%	30
Noblett (92)	2006	ODM	Intra	FTc	Abdominal	103	0.0%	52	2.0%	51
Osawa (93)	2016	LiDCO	Intra	CI	Cardiothoracic	126	4.8%	62	9.4%	64
Parke (94)	2015	FloTrac	Post	SVV	Cardiothoracic	144	0.0%	70	1.4%	74
Pavlovic (95)	2016	PiCCO	Intra	PPV	Other	43	25.0%	20	13.0%	23
Pearse (96)	2005	LiDCO	Post	SVV	High risk	122	14.5%	62	11.7%	60
Pearse (97)	2014	LiDCO	Intra/post	SVmax	Abdominal	733	3.3%	368	3.0%	365
Peng (98)	2014	FloTrac	Intra	SVV	Orthopaedic	80	2.5%	40	0.0%	40
Pestaña (99)	2014	NICOM	Intra/post	CI	Abdominal	142	4.2%	72	5.7%	70
Phan (100)	2014	ODM	Intra	FTc	Abdominal	100	0.0%	50	4.0%	50
Picard (101)	2016	ODM	Intra	FTc	Neuro	67	N/A	33	N/A	34
Pillai (102)	2011	ODM	Intra	SVV	Abdominal	66	N/A	32	N/A	34
Pölönen (103)	2000	PAC	Post	SVO_2	Cardiothoracic	393	1.5%	196	3.6%	197
Pösö (104)	2014	TTE/FloTrac	Pre/intra	SVV	Abdominal	46	0.0%	26	0.0%	20
Ramsingh (105)	2013	FloTrac	Intra	SVV	Abdominal	40	0.0%	20	0.0%	20
Reisinger (106)	2017	ODM	Intra/post	SVmax	Abdominal	58	0.0%	27	3.2%	31
Salzwedel (107)	2013	ProAQT	Intra	PPV	Abdominal	160	0.0%	79	0.0%	81
Sandham (108)	2003	PAC	Intra	DO_2	High risk	1,994	16.3%	997	15.5%	997
Senagore (109)	2009	ODM	Intra	SVV	Abdominal	64	2.4%	42	0.0%	22
Sethi (110)	2017	CVL	Intra	CVP	Abdominal	94	4.3%	46	18.8%	48
Shoemaker (12)	1988	PAC	Pre/intra/post	CI	High risk	88	3.6%	28	28.3%	60
Scheeren (111)	2013	FloTrac	Intra	SVV	High risk	52	0.0%	26	7.7%	26
Schmid (112)	2016	PiCCO	Intra/post	GEDVI	Abdominal	180	23.9%	92	18.2%	88
Schultz (113)	1985	PAC	Pre/intra/post	CI	Orthopaedic	70	2.9%	35	28.6%	35
Sinclair (114)	1997	ODM	Intra	FTc	Orthopaedic	40	5.0%	20	10.0%	20
Smetkin (115)	2009	PiCCO	Intra	ITBVI	Cardiothoracic	40	0.0%	20	0.0%	20
Stens (116)	2017	Nexfin	Intra	PPV	Abdominal	175	1.2%	81	1.1%	94
Szakmany (117)	2005	PiCCO	Intra	ITBVI	Abdominal	40	10.0%	20	5.0%	20
Szturz (118)	2019	ODM	Intra	CI	Abdominal	140	1.4%	71	1.4%	69
Thomson (119)	2014	LiDCO	Post	SVmax	Cardiothoracic	264	1.6%	123	1.4%	141
Torregiani (120)	2018	FloTrac	Intra	SVV	Abdominal	147	N/A	71	N/A	76
Ueno (121)	1998	PAC	Post	CI	Liver	34	0.0%	16	11.1%	18
Valentine (122)	1998	PAC	Pre/intra/post	CI	Vascular	120	5.0%	60	1.7%	60

Table 2 *(continued)*

Table 2 *(continued)*

Author	Year	Device	Timing	Target variable	Type	Total number of patients	Mortality pGDT	Number of patients in pGDT arm	Mortality controls	Number of controls
Van der Linden (123)	2010	FloTrac	Intra	CI	Vascular	37	15.0%	20	0.0%	17
Velmahos (124)	2000	Bioimpedance	Pre/intra/post	SBP	Trauma	75	15.0%	40	11.4%	35
Venn (125)	2002	ODM	Intra	FTc	Orthopaedic	59	10.0%	30	6.9%	29
Wakeling (126)	2005	ODM	Intra	SVV	Abdominal	128	0.0%	64	1.6%	64
Wenkui (127)	2010	Laboratory	Post	Lactate	Abdominal	214	0.9%	109	3.8%	105
Wilson (128)	1999	PAC	Pre/intra/post	PAOP	High risk	138	3.3%	92	17.4%	46
Wu (129)	2017	FloTrac	Intra	SVV	Neuro	63	N/A	33	N/A	30
Xiao (130)	2015	LiDCO	Intra	SVmax	Other	98	N/A	49	N/A	49
Xu (131)	2017	FloTrac	Intra	SVV	Thoracic	168	N/A	84	N/A	84
Yassen (132)	2012	PAC	Post	SVmax	Liver	53	13.9%	36	17.6%	17
Yin (133)	2018	NICOM	Intra	SVV	Abdominal	45	N/A	22	N/A	23
Yu (134)	2015	Masimo/PVI	Intra	PVI	Abdominal	30	N/A	15	N/A	15
Zakhaleva (135)	2013	ODM	Intra	FTc	Abdominal	72	0.0%	32	0.0%	40
Zeng	2014	FloTrac	Intra	SVV	Abdominal				Retracted article	
Zhang (136)	2013	FloTrac	Intra	SVV	Cardiothoracic	60	N/A	30	N/A	30
Zhang (137)	2012	Datex	Intra	PPV	Abdominal	60	0.0%	40	0.0%	20
Zheng (138)	2013	FloTrac	Intra	CI	Abdominal	60	0.0%	30	0.0%	30
Ziegler (139)	1997	PAC	Pre	PAOP	Vascular	72	9.4%	32	5.0%	40
Total	–	–	–	–	–	14,009	4.6%	7,027	7.5%	6,982

pGDT, perioperative goal directed therapy; PAC, pulmonary artery catheterisation; ODM, oesophageal Doppler monitoring; PVI, Pleth Variability Index; CVL, central venous line; OD, oesophageal Doppler; NICOM, noninvasive cardiac output monitoring; TTE, transthoracic echocardiogram; SVV, stroke volume variation; PPV, pulse pressure variation; SVmax, maximal stroke volume; DO_2, oxygen delivery; CI, cardiac index; SPV, systolic pressure variation; PVI, Pleth Variability Index; O_2ER, oxygen extraction ratio; GEDVI, global end-diastolic volume index; MAP, mean arterial pressure; $ScVO_2$, central venous oxygen saturation; SVO_2, mixed venous oxygen saturation; ITBVI, intrathoracic blood volume index; SBP, systolic blood pressure; PAOP, pulmonary artery occlusion pressure; N/A, not available.

bring no more additional value.

Oesophageal Doppler technology (OED) is probably the second most important pGDT monitoring device. It was the first that replace the PAC in many countries, and the pGDT is virtually associated with OED. The National Institute for Health and Care Excellence (NICE) guidelines (141) has implemented OED monitoring into the national-wide healthcare program. Up to day, 25 studies have been published using the OED technology, in which 2,709 patients were included. Its use is less invasive and has minimum contraindications, though sometimes it could be difficult to obtain the good acoustic window and performance of the device may be disturbed by the ongoing surgery. The CI/SV measurement is relatively accurate (142) and offers specific parameters of fluid response [corrected flow time (FTc)] and contractility (mean acceleration or peak velocity). Hence, the OED enables parallel assessment of individual heart performance determinants—as demonstrated by Szturz recently (118).

Devices based on pulse wave analysis (PWA) represent the largest and most frequently used group. They have been used in 51 RCTs so far and they are base for several ongoing multicentric RCTs (143,144) (plus the @OPTIMISE2trial). The simplicity to use (virtually "plug-and-play") make them ideal for pGDT in intermediate to high-risk surgical patients. Most of uncalibrated PWA technologies have

been repeatedly questioned in terms of the reliability (accuracy and precision); but it seems the tracking ability is good enough to enable pGDT (145,146). Besides, the use of PWA is mostly coupled with the use of dynamic variations of pulse pressure or SV as markers of preload responsiveness.

Non-invasive devices are currently the most controversial group of monitors. First, the group is extremely heterogeneous and the devices are based on different principles (volume clamp method of blood pressure curve reconstruction, thoracic bioimpedance or bioreactance, Fick principle and multiple others). This complete non-invasiveness virtually enables widespread use, even for patients in low-to-intermediate risk, because they are not associated with any potential harm. However, accuracy and precision of these devices has been repeatedly questioned (146,147), even though the population tested is not entirely matching the target population [mostly high-risk or intensive care patients—for further reading see (148)]. Among screened studies 13 RCTs used some sort of non-invasive technology (10 out of them has been published during or after 2015). In four RCTs the non-invasive blood pressure analysis with following non-calibrated cardiac output calculation has been used (hence are more an extension of PWA devices). In three other studies, Massimo rainbow pulse oximeter and its Pleth Variability Index (PVI) parameter has been used hence only fluid based pGDT was affordable. Finally, bioimpedance or bioreactance technology has been used in six another RCTs.

Treatment goals and means

Cardiac output/index is historically the most important and reasonable treatment target of pGDT protocols. Coupled with hemoglobin concentration it creates the physiological rationale for improving the peripheral tissue oxygen supply. However, the actual value of CI target significantly varies among studies. The original work of Shoemaker and colleagues (12) aimed for "supranormal" CI of 4.5 L/min/m^2—goal not easily to reach in high-risk patients without using inotropic support. In later RCTs only normal values (i.e., around 3.0 L/min/m^2) were used as target and most recently concept of "avoid-the-low CI" was used (i.e., above 2.0 or 2.5 L/min/m^2). Patients in the intermediate-risk group usually need only preload optimization to reach these conservative targets. Therefore, further inotropic support is necessary only in minority of patients and should be limited for high-risk patients or those with unexpectedly low cardiac performance. Individualization of the target CI base on preoperative echocardiography or by other non-invasive measurements may be and interesting option for the future.

SV/SV index as a treatment target is mostly used to improve the heart preload. The NICE/National Health Service (NHS) guidelines-based protocol (149) recommend a stepwise SV maximization process: a step/volume challenge of 200–250 mL is given with reassessment. At least 10% increase in SV after volume challenge is taken as a positive response that prompts a repetition of volume challenge. The goal is to reach a state of fluid unresponsiveness by sequential volume loading steps. If any decrease in SV larger than 10% occurs later on, a volume challenge should be repeated to keep maximal SV conditions. Interestingly, the other factors affecting the SV (contractility or afterload changes) are frequently neglected. In addition, in patients with good CV reserve, the maximization of SV seems not to be associated with improved outcomes (62). It seems that reaching fluid unresponsiveness by SV maximization may lead to unnecessarily high amount of intravenous fluids administration with all its negative consequences (especially considering the vasodilatory effect of anesthetics).

Variation of SV, pulse pressure or plethysmography-variability index create together one large group of so-called "dynamic preload parameters"—parameter yet unbeaten in terms of predictive potential for testing preload reserve under generally known and acceptable conditions (i.e., absence of spontaneous breathing, tidal volume of more than 8 mL/kg of ideal body weight, absence of arrhythmias, etc.) (150-152). Fluid optimization guided by these parameters has been associated with improved outcomes based on meta-analysis of 14 studies (9). Naturally, these parameters may be used for optimizing the fluid load only, thus they have to be coupled with parameters assessing oxygen delivery adequacy and afterload.

Among Doppler-based parameters, the FTc has gained most attention as a parameter for guiding preload optimization. Other parameters (SV, CI and/or peak velocity) are usually used for complex assessment of hemodynamic status and further optimization. Low specificity of FTc and its dependence on afterload and some demographic parameters (i.e., age, sex) are drawbacks of this approach. Contrary, peak velocity is currently the most appropriate parameter to assess the contractile function. In a recent RCT by Szturz such complex approach with the use of FTc to asses fluid needs, peak velocity to modulate contractility by dobutamine and blood pressure product (systemic resistance) to use vasoactive medication has been associated with improved outcomes in

abdominal surgery (118).

Blood pressure is often overlooked target of the pGDT protocols. Adequate perfusion of vital organs is maintained by body regulatory mechanism throughout large scale of perfusion pressures via its natural autoregulatory mechanisms. However, these mechanisms may put the peripheral tissues (including gastrointestinal tract or muscles) perfusion in danger. Maintaining adequate cardiac output is the first step of pGDT, but may endanger local flow through some organs when not coupled with adequate perfusion pressure. Currently number of large-scale retrospective studies exist to support that even short periods of hypotension are associated with postoperative complications (153-156). In one prospective RCT maintaining adequate perfusion pressure was associated with improved outcomes in patients with arterial hypertension (157). However, based on data by Saugel *et al.* (158), defining the adequate individual perfusion pressures is not that straightforward, because widely used pre-anesthesia values are far from being accurate surrogate.

Limitations and adoption roadblock

Even though pGDT is currently based on number of positive RCTs and is proposed by several national (or multinational) guidelines, its adoption into real praxis is still challenging (159,160). Recent surveys among anesthesiologists from diverse countries indicates that "pressure monitoring only" is still the prevailing praxis (160-162). Following reasons are major limits in adoption of pGDT:

(I) Lack of high-level evidence—though we do possess a number of individual RCTs proving a beneficial effect, their heterogeneity precludes to draw any hard conclusions. Besides, the studies demonstrating more benefit are those smaller, with high risk of bias; while large, multi-centric studies often do not prove this (97,99,108).

(II) Lack of clear-cut approach—the heterogeneity of approaches, devices and treatment targets precludes giving a clear-cut recommendation in whom, using what device, which variable and which target value should be used (163).

(III) Uncertain cost-benefit—most of monitoring technologies used for pGDT are associated with non-deniable economic burden, the use of pGDT further increases the demands on treating staff leading to increased economic (and personal) costs. Contrary, the benefit of pGDT is postponed and observed in a large-scale view only (available to hospital administrators). Several studies tried to overcome this by putting the results of different RCTs into economical context (164,165), but on individual basis the economic restrains still exists.

Future perspectives

Based on the current evidence pGDT seems to be a rational concept of perioperative care for intermediate-to-high-risk surgical patients. Further development is necessary to overcome most of the uncertainties and roadblocks. Currently three multicentric studies are ongoing [GAS-ART (143), iPEGASUS (144) and OPTIMISE II], which may put some more light on the effectivity of pGDT approach in the context of current perioperative care. However, several concerns could be raised regarding protocols of these trials. A pragmatic fixed dose of inotrope used in OPTIMISE II, SV maximization in GAS-ART (143) do repeat previous attempts but on larger scale. A true individualization should reflect patient's long-term normal values and reserves, but such protocol has not been tested yet.

Another factor may further help us to design rational individualized pGDT trials in the future. First, the development of non-invasive monitoring tools may enable us to assess the individual target values much more easily. A cumbersome ambulatory oscillometric cuff blood pressure measurement would be replaceable by some of novel technologies for monitoring not only blood pressure but blood flow as well. Hemodynamic profile of individual patient obtained in preoperative period may set the base for perioperative hemodynamic targets. Second improvement, which is on the way, are novel, more specific parameters for individual determinants of cardiac function. Parameters as dynamic elastance, change in arterial pressure in time during upstroke and other parameters may further improve our understanding of the underlying pathology. Finally, the introduction of artificial intelligence and automated closed-loop systems may further help the implementation of pGDT. Recently marketed algorithm seems to be able accurately predict development of spontaneous hypotension in following 5–10 minutes (166,167). This enables the treating team either to get ready or to pre-react, hypothetically enabling to decrease hypotensive periods. Other much simpler algorithms were tested to enable closed-loop systems for decision support for individualized pGDT (68,168).

Putting these entire improvements together one may propose the further design of pGDT approach:

(I) Based on large scale studies individual patients or small adequately defined populations may be picked out to have profit out of pGDT intervention. A stepwise approach defined by patient risks, surgical intervention and other variables is advisable.

(II) Preoperative noninvasive testing of the individual CV (and other) system capacity may help to set the proper individual target values. Active approach may be set up for the high-risk patients.

(III) Based on our better understanding of CV system artificial intelligence may be incorporated in decision making process helping the treating physician to pick up the treatment of choice by and making further decision more precise and individualized.

Conclusions

pGDT is one of the possibilities to improve postoperative outcome of intermediate-to-high risk surgical patients. Based on current evidence it seems to be associated with decreased postoperative length of stay, number of complications and possibly even mortality (in the high-risk population). However, the current evidence is extremely heterogeneous because of large time-span between individual RCTs, monitoring technologies and treatment targets used.

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Footnote

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