Arterial Waveform Analysis Reflects Cardiac Output Changes Following Pneumoperitoneum

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ABSTRACT

Rationale: Cardiac output (CO) response to pneumoperitoneum is difficult to predict because of multiple, often contradictory physiologic effects. It remains uncertain whether arterial waveform variables can predict changes in CO during pneumoperitoneum. We hypothesized that changes of arterial waveform variables following pneumoperitoneum will correlate with CO changes.

Objectives: Patients scheduled for major elective laparoscopic surgery were recruited to the study. CO and stroke volume variation (SVV) were continuously monitored by non-invasive cardiac output monitor (NICOM). Arterial waveforms were recorded before and during pneumoperitoneum of 15 mmHg. Systolic and pulse pressure variations (SPV and PPV) were determined offline.

Findings: Pneumoperitoneum resulted in minimal changes in heart rate and mild increase of mean arterial blood pressure and pulse pressure. Cardiac output decreased significantly following pneumoperitoneum, while SPV and its delta down (dDown) component increased by 34 and 23%, respectively. Changes in SVV and PPV were not significant. Baseline SPV, PPV and dDown correlated weakly with changes in CO caused by pneumoperitoneum. Changes in dDown and PPV following PnP correlated with changes in CO ($r=-0.385$, $P=0.002$; $r=-0.274$, $P=0.034$, respectively), while those in SPV and SVV did not.

Conclusion: Our study has shown that CO changes following pneumoperitoneum are preload dependent. Arterial waveform variables, especially dDown, correlated significantly with changes in CO during pneumoperitoneum.

Introduction
Cardiac output (CO) response to pneumoperitoneum is unpredictable even within similar groups of patients [1-5]. Pneumoperitoneum may increase CO due to recruitment of splanchnic venous blood [5]; however, higher levels of pneumoperitoneum may hinder venous return due to direct compression of the inferior vena cava leading to reduced venous return and CO [6-8].

Arterial waveform analyses have been shown repeatedly to identify acute hypovolemia [9,10], and to predict CO response to fluid loading [11]. The usefulness of waveform analysis for the estimation of CO changes following pneumoperitoneum is less clear. Decreases in CO due to pneumoperitoneum were effectively reversed with head down tilt, suggesting preload dependent changes in CO [3,4].

We hypothesized that the dominant hemodynamic effect of pneumoperitoneum of 15 mmHg is a reduction of preload which can be estimated by arterial waveform variables. Therefore, patients with elevated values of waveform variables [9], who are potentially more sensitive to preload reduction, will develop a greater reduction in CO following pneumoperitoneum. We also hypothesized that changes of arterial waveform variables following pneumoperitoneum will correlate with CO changes. The objectives of our study were: a) to evaluate whether arterial waveform variables before pneumoperitoneum correlate with CO changes following pneumoperitoneum, and b) to evaluate the relationship between changes in waveform variables and changes in CO following pneumoperitoneum.

Methods
The study was approved by the institutional ethic board (Helsinki committee, ref. CMC-12-0133) and registered in ClinicalTrial. gov (ref. NCT01867814). Written informed consent was obtained from all participants. Patients who were 18 years old or older, with an ASA class of I-III who were scheduled for major elective laparoscopic surgery (partial hepatectomy, pancreatectomy, colectomy) were recruited to the study. Patients with cardiac rhythm different from sinus were excluded.

All participants were premedicated with oral Diazepam 10 mg at the morning of surgery in addition to chronic treatment by beta-adrenergic antagonists. ACE-inhibitors were skipped on the day of surgery.

The patients were anesthetized with Fentanyl 1-2 mcg kg^{-1}, Propofol 2-3 mg kg^{-1} and Rocuronium 0.6-1 mg kg^{-1} followed by endotracheal intubation and mechanical volume-controlled ventilation with VT=8 ml kg^{-1} of ideal body weight. Anesthesia was maintained by inhalation of O_2/Air (FiO$_2$=0.4-0.5) with 0.6-1.3 MAC of isoflurane and intermittent boluses of Fentanyl and Rocuronium according to the bispectral index (BIS) and neuromuscular monitoring (modules of AS3 monitor, Datex, Helsinki, Finland).

The arterial blood pressure was directly measured using 20 GA radial artery catheter (BD Venflon, Becton Dickinson Infusion Therapy AB, Helsingborg, Sweden). Cardiac output (CO), stroke volume (SV) and stroke volume variation (SVV) were continuously monitored by non-invasive cardiac output monitor (NICOM, Cheetah Reliant, Cheetah Medical (UK) Limited, Maidenhead, Berkshire, UK).

All values were registered twice, first time two minutes after insertion of intraperitoneal Veres needle (before gas insufflation) and second time two minutes after intraabdominal pressure reached 15 mm Hg. The values of CO, SV and SVV were recorded. Arterial pressure curve was recorded at the speed of 1 mm sec^{-1} using module of AS3 monitor (Datex, Helsinki, Finland) during 4-5 respiratory circles followed by 15 sec apnea. Arterial pressure variables, systolic pressure variation (SPV), delta up (dUp) and delta down (dDown) components as well as pulse pressure variation (PPV) were measured and calculated offline.

Measurements of waveform variables (SPV, dUp, dDown, pulse pressures) have been made as following technique. The recorded waveform of arterial pressure curve was scanned at 300 dpi resolution and exported to Microsoft Word document file (Microsoft Office 2010; Microsoft Co., Redmond, WA, USA) as JPEG pictures (Figure 1). Parallel horizontal lines (black) were drawn through the points of systolic pressure during apnea, maximal and minimal systolic and diastolic pressures during respiratory circle. The connecting vertical lines (solid red) designate the variables. Manual measurements of the length of the connecting lines were made using the format shape function. Conversion of length to pressure value has been made proportionally to length of the line designating pressure of 75 mm Hg (dash red) measured by the same method. Average values of 3 consecutive complexes were taken. PPV was calculated as a difference between maximal and minimal pulse pressure during single respiratory cycle normalized to pulse pressure average.
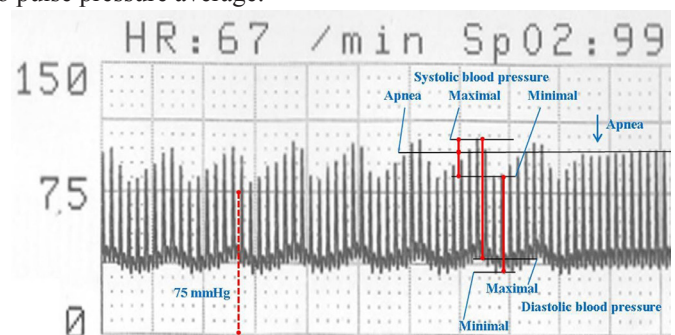

Figure 1: Arterial blood pressure variables measurements.

Statistical Analysis
Statistical analysis was performed by using IBM statistics (SPSS),

version 24. The continuous variables were presented by mean, median and standard deviation. The categorical variables were presented in percentages. Differences in clinical parameters before and after insufflation were compared using Paired t-test or Wilcoxon sign rank test, as appropriate. Correlations between the clinical parameters before inflation and CO, SV after inflation and correlations between the parameter's differences were analyzed using Pearson or Spearman correlation, as appropriate. $P < 0.05$ was considered statistically significant.

Results

A total of sixty-three patients were recruited into the study. The demographic details of the patients are presented in Table 1. Two patients were withdrawn from the study due to an arrhythmia which developed after anesthesia induction and one patient due to technical problems with arterial waveform recording. The depth of anesthesia (according to the BIS) remained unchanged during the two stages of the study. Peak inspiratory airway pressure increased significantly after CO_2 insufflation (Table 2). Expired CO_2 was kept stable (F_ECO_2 at 35-37 mm Hg) by adapting respiratory rate.

No of patients		60
Males / Females		23 / 37
Age (years)		64.6 ± 14.9
BMI (kg m^{-2})		28.5 ± 5.1
ASA Class (I / II / III)		5 / 41 / 14
Surgery	Partial Hepatectomy	7
	Pancreatectomy	2
	Colectomy	51
Medical history	CHF	4
	HTN	42
	COPD	4
	PVD	2
	CRF	13
	DM	27
	BMI > 30	21
Chronic medications	β-adrenergic antagonists	22
	ACE-inhibitors	27
	Ca-channel blockers	16
	Diuretics	13
	α$_2$-adrenergic agonists	3

Table 1: Demographic data.
CO= Cardiac Output; BMI= Body Mass Index; ASA= American Society of Anesthesiologists; CHF= Congestive Heart Failure; HTN= Hypertension Disease; COPD= Chronic Obstructive; Pulmonary Disease; PVD= Peripheral Vascular Disease; CRF= Chronic Renal Failure; DM= Diabetes Mellitus; ACE= Angiotensin Converting Enzyme.

Pneumoperitoneum resulted in minimal changes in heart rate (HR), mild increase of mean arterial blood pressure (MBP) and pulse pressure (PP) (Table 2). Cardiac output and SV decreased significantly following pneumoperitoneum. SPV and dDown increased following PnP by 34 and 23%, respectively. SVV decreased minimally while PPV did not change (Table 2).

Prediction of cardiac output changes from baseline variables

Baseline values of HR, MBP and PP did not correlate with changes of CO after pneumoperitoneum. Baseline waveform variables, other than SVV, correlated weakly with changes in CO (Table 2).

Variables	All patients (n=60)			Correlation: Variables at PnP=0 and CO Changes	
	PnP=0 mmHg	PnP=15 mmHg	p-value	Correlation coefficient	p-value
PIP (cmH$_2$O)	19.1 ± 2.8	25.0 ± 3.8	< 0.0001	0.24	0.06
HR (b/min)	65.8 ± 13.2	67.5 ± 14.0	0.1	-0.07	0.6
MAP (mmHg)	59.3 ± 9.0	72.4 ± 14.0	< 0.0001	0.11	0.4
PP (mmHg)	44.5 ± 9.3	48.3 ± 14.5	0.01	-0.03	0.9
CO (L/min)	5.9 ± 1.4	5.6 ± 1.4	0.03	-	-
SV (mL)	89.3 ± 22.6	84.1 ± 20.4	0.0001	0.21	0.10
BIS	43.0 ± 7.4	42.2 ± 7.3	0.4	-	-
SPV, mmHg	6.5 ± 3.0	8.7 ± 3.2	< 0.001	-0.32	0.01
dDown, mmHg	4.0 ± 2.8	4.9 ± 2.9	0.03	-0.31	0.02
PPV, %	10.1 ± 6.0	10.9 ± 5.5	0.3	-0.27	0.03
SVV, %	8.9 ± 2.8	8.1 ± 2.7	0.005	-0.002	1.0

**Table 2:** Variables during pneumoperitoneum.
PnP= Pneumoperitoneum; PIP= Peak Inspiratory Pressure; HR= Heart Rate; MAP= Mean Arterial Pressure; PP= Pulse Pressure; CO= Cardiac Output; SV= Stroke Volume; BIS= Bispectral Index; SPV= Systolic Pressure Variation; dDown= delta Down Component of SPV; PPV= Pulse Pressure Variation; SVV= Stroke Volume Variation.

Correlation of changes in hemodynamic variables following PnP

Heart rate changes following pneumoperitoneum correlated with changes in CO (r=0.372, P=0.003), while changes in MBP and PP did not. Changes in dDown and PPV correlated with changes in CO (r=-0.385, P=0.002; r=-0.274, P=0.034, respectively) (Figures 2 and 3), while those in SPV and SVV did not.

r = - 0.4
p = 0.002
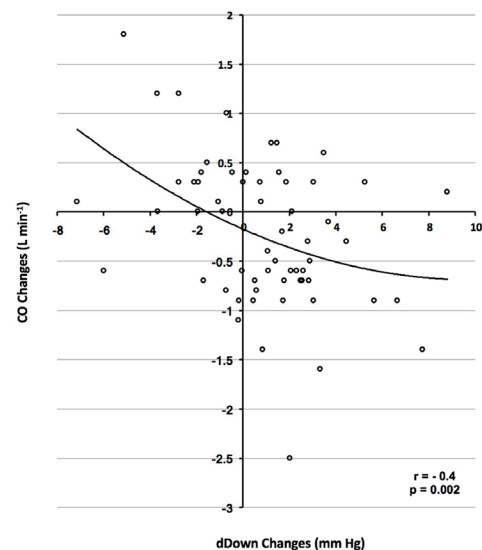
Figure 2: Correlation between changes in dDown and changes in cardiac output.
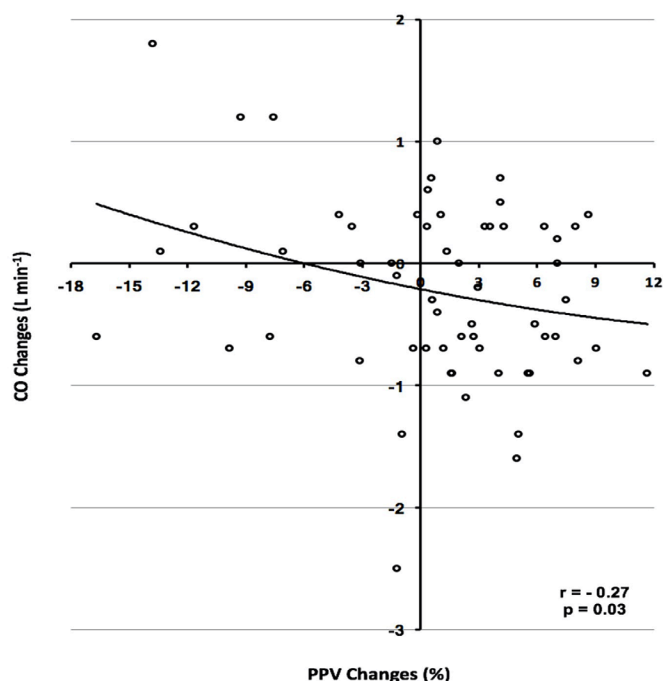
Figure 3: Correlation between changes in pulse pressure variation and changes in cardiac output.

Additional analysis

For further analysis patients were separated into three groups according to changes in CO following pneumoperitoneum: those whose CO decreased by at least 10% after PnP (n=20), those whose CO increased by at least 10% (n=6) and those whose CO did not change (CO changes by 10% or less (Table 3). The average magnitude of CO changes in both directions, were about 20% from baseline values (Table 3).

There were similar changes in peak inspiratory pressure (PIP), HR, MBP and PP in patients with decreased, increased or unchanged CO. SPV increased significantly in all patients except those in whom CO increased secondary to pneumoperitoneum. The dDown remained unchanged in patients without changes in CO, increased

significantly (by 56%) in patients with decreased CO and showed a tendency to decrease (by 30%, P=0.08) in patients in whom CO increased. PPV did not change significantly in any of the three subgroups of patients. SVV decreased slightly in all patients and this change was statistically significant only in patients without changes in CO.

Variables	Decreased CO (n=20)		No Changes in CO (n=34)		Increased CO (n=6)	
	PnP=0 mmHg	PnP=15 mmHg	PnP=0 mmHg	PnP=15 mmHg	PnP=0 mmHg	PnP=15 mmHg
PIP (cm-H_2O)	19.8 ± 3.3	26.5 ± 4.2*	18.9 ± 2.5	24.5 ± 3.6*	17.5 ± 1.5	23.3 ± 1.6*
HR (b/min)	63.1 ± 14.0	61.8 ± 11.1	66.2 ± 12.1	68.8 ± 13.0†	72.7 ± 15.4	79.2 ± 20.5
MAP (mmHg)	59.8 ± 8.0	72.2 ± 12.6*	58.9 ± 10.2	72.0 ± 14.8*	60.6 ± 2.8	74.9 ± 15.4
PP (mmHg)	45.3 ± 10.0	46.7 ± 15.6	43.3 ± 9.4	49.3 ± 13.6*	48.2 ± 5.7	48.5 ± 18.1
CO (L/min)	6.0 ± 1.0	5.0 ± 0.9*	5.9 ± 1.6	5.9 ± 1.5	5.2 ± 1.1	6.3 ± 0.9*
SV (mL)	92.4 ± 14.6	79.3 ± 12.5*	90.1 ± 25.2	87.4 ± 22.7‡	74.8 ± 27.0	81.3 ± 27.6*
SPV (mmHg)	5.8 ± 2.6	8.6 ± 2.3*	6.5 ± 2.5	8.5 ± 3.1*	9.4 ± 5.4	10.5 ± 5.5
dDown (mmHg)	3.4 ± 2.3	5.3 ± 2.3*	3.8 ± 2.2	4.6 ± 3.0	7.1 ± 5.3	5.0 ± 4.4‡
PPV (%)	8.8 ± 5.4	11.0 ± 4.3	9.7 ± 5.1	10.5 ± 5.8	15.9 ± 9.5	12.3 ± 7.8
SVV (%)	9.4 ± 2.4	8.8 ± 2.8	8.8 ± 3.0	7.9 ± 2.7*	8.3 ± 3.1	7.2 ± 1.2

Table 3: Variables during pneumoperitoneum – according to the cardiac output changes.
PnP= Pneumoperitoneum; PIP= Peak Inspiratory Pressure; HR= Heart Rate; MAP= Mean Arterial Pressure; PP= Pulse Pressure; CO= Cardiac Output; SV= Stroke Volume; SPV = Systolic Pressure Variation; dDown= delta Down Component of SPV; PPV= Pulse Pressure Variation; SVV= Stroke Volume Variation.
Comparison between variables at PnP of 0 and 15 mmHg: * - p < 0.05; † - p = 0.07; ‡ - p = 0.08.

Discussion

This study has shown that in more than 40% of our patient's CO changed significantly as result of pneumoperitoneum. In one third of the patients CO decreased by 17%. These results emphasize the importance of CO measurement, which is not performed routinely even during extensive surgery [12]. This study found that changes in CO cannot be predicted from changes in "conventional" hemodynamic parameters. Automated waveform analysis (SPV and PPV) corresponded with changes in CO; this association was the strongest with the dDown component of SPV.

During pneumoperitoneum preload increases at the beginning of intraabdominal CO2 insufflation, followed by a reduction of venous return due to several factors including impairment to inferior vena cava flow, increase in left ventricular afterload and complex humoral response to intraabdominal pressure [13]. These

hemodynamic changes can affect differently patients with different baseline volume status and variable blood reserve which can be potentially mobilized from the splanchnic circulation – unstressed volume [5,8]. It has been shown that decreases in preload result in a rise in waveform variables during pneumoperitoneum as well as in other surgical populations requiring mechanical ventilation [14,15]. We suggest that more prominent increase in arterial blood pressure waveform variables in patients who decrease CO in our study is due to a greater decrease in venous return in these patients. These results support our hypothesis that increased waveform variables are associated with a reduction in CO.

The dDown component of SPV, expresses the decrease in stroke volume that results from diminished venous return following increased intrathoracic pressure during mechanical inspiration [16,17]. In patients who suffered a decrease in CO following

pneumoperitoneum dDown increased significantly mainly because the increase in intraabdominal pressure created a resistance to venous return. The Starling resistor of venous blood flow could appear at different pneumoperitoneum pressures in different patients [6,7]. Therefore, in the present study dDown was probably increased in patients with a decrease in CO, due to the Starling resistor mechanism, creating relative central hypovolemia. On the other hand, patients with a decrease in dDown were those with increased CO, probably due to augmented venous return following squeezing of the splanchnic vessels, i.e. mobilization of unstressed volume [5]. The PPV presented with similar changes, however, these were not statistically significant. It has been shown previously that the decline of CO following pneumoperitoneum can be reversed by head-down positioning supporting the preload dependency mechanism of CO changes following increased intraabdominal pressure [3,4].

Our findings of changes of the SPV and PPV after pneumoperitoneum support previous studies, SPV increased significantly due to pneumoperitoneum and PPV changed very little [1,4,14]. Both variables correlated with CO changes although these changes were less prominent than dDown. The association between changes in either SPV or PPV and CO was weaker than the association between changes in dDown and CO. SPV was less accurate in predicting changes in CO than its dDown component, because the dUp component of SPV is related to increased airway pressure during mechanical ventilation rather than to changes in preload [18]. Most of the PPV values observed during the study were in and around the "grey zone" and for that reason they were weak predictors of changes in CO [19]. Similar only minimal changes in PPV due to pneumoperitoneum have been shown in several studies [1,14].

We have difficulty in explaining the lack of corresponding changes in SVV following pneumoperitoneum. One of the potential explanations may be the method of measuring stroke volume by NICOM; however, similar lack of changes in SVV following pneumoperitoneum has been found using both the Vigileo system (Edwards Lifesciences; version 03.02) and esophageal Doppler [1]. In contrast, Rosendal and colleagues found an increase in both SVV and PPV using transpulmonary thermodilution [4].

The population of our study is representative of the general adult elective surgical population. The baseline SPV and PPV values were similar to those found in a previous study with elective population [9] and the finding of a retrospective analysis of a large general surgery population [20].

Limitations
The major limitation of the study is that we didn't measure heart preload or venous return. Venous return can be assessed by measuring flow in the inferior vena cava; however, this measurement is complex in clinical setting.

An accurate measurement of left ventricular preload with echocardiography would obviously give us additional information about preload changes; however, diaphragmatic displacement due to pneumoperitoneum is expected to hinder this measurement.

The accuracy of NICOM measurement of CO has been evaluated recently and although the measurement may not be accurate over a long-time period [21], it is accepted as satisfactory for trends [22]. In our study all measurements lasted no more than 10 minutes and we were following only changes in CO rather than absolute values.

Another limitation is that we did not perform any demographic analysis for potential interaction of pneumoperitoneum affect and waveform analysis because of the small sample size. Such an interaction between chronic beta-adrenergic antagonist therapy and waveform variables was recently shown in a large population study [20].

In conclusion, arterial waveform variables, especially dDown, correlated significantly with changes in CO after pneumoperitoneum. The dDown component increased in patients who presented with a decrease of CO and decreased in those in whom CO increased. These changes in dDown and CO reflect preload dependency of CO during pneumoperitoneum.

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