Pharmacodynamic modeling of changes in pulse waveform during induction of propofol anaesthesia in volunteers: comparison between invasive and continuous non-invasive measurements of pulse pressure

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Introduction: Propofol anaesthesia causes changes in pulse pressure waveform. Features of pulse pressure waveform from radial artery are associated with blood flow properties of central arteries and left ventricular heart function.[1, 2] Since maintenance of stable hemodynamics is one of the main goals of adequate anaesthesia, non-invasive monitoring of pulse waveform parameters may contribute additional information to routine measurement of arterial blood pressure.
Continuous non-invasive finger blood pressure recordings performed with Task Force Monitor® (TFM) provide real-time pulse pressure waveforms. In this exploratory study, we estimated propofol induced changes in three pulse waveform parameters during induction of anaesthesia by pharmacokinetic/-dynamic (Pk/Pd) modeling and examined whether Pd parameters fitted with non-invasive measurements were similar to those fitted with invasive measurements from radial artery.
Methods: After local ethics committee approval we studied 9 volunteers of ASA I. Propofol was infused via target controlled infusion to achieve plasma concentrations increasing from 0.5 to 4.5 µg/ml in steps of 0.5 µg/ml. Each infusion step was maintained constant for at least 15 minutes. Following the last step, propofol was further linearly increased by 0.5 µg/ml·min, until one of the following conditions was present: EEG suppression > 2 s, flattening of spontaneous breathing, or mean blood pressure drop > 45% from baseline.
Pulse pressure (PP), average change in pulse pressure ($dPdT_{max}$), and area under diastolic curve (AUC_{diast}) (Fig.1) were derived from valid pulse pressure beats that were recorded from continuous invasive radial (ALINE) and non-invasive TFM measurements of same upper extremity. The relation between drug dosing and time course of pulse waveform parameters was modeled using a Pk/Pd model with a common sigmoid concentration-effect relationship in which EC_{50} is the concentration for half-maximum effect, and γ (gamma) exponent describes the steepness of the concentration effect. We expressed the propofol effect on pulse waveform parameter (P) in each volunteer as the percent decrease from baseline: $P(t) / P_{baseline} \times 100 = 100 - [100 \times C_e(t)^{\gamma}] / EC_{50}^{\gamma} + C_e(t)^{\gamma}]$. $C_e(t)$ is the effect site concentration obtained by differential equation $dC_e / dt = (C_{pl} - C_e) \cdot k_{e0}$, whereby C_{pl} is measured plasma concentration of propofol, and k_{e0} denotes the first-order rate constant determining the efflux from the effect-site.[3] The goodness of the pharmacodynamic fit was assessed by the unweighted residuals $R=(E_M-E_P)/E_0 \times 100\%$ and the absolute residuals $AR=(|E_M- E_P|)/E_0 \times 100\%$ from E_0, E_M, and E_P as baseline, measured and predicted effect, respectively. Significant differences between ALINE and TFM were identified by Wilcoxon signed-rank test. The fitting procedure and statistical calculations at a significance level of $\alpha=0.05$ have been performed with Matlab (Version 2009a, The Mathworks Inc., Natick, MA, USA). Data are presented as mean±SD (median).

Results: Propofol induced a significant decrease in PP, dPdTmax, and AUCdiast (Tab. 1, Fig.2). Fig. 3 depicts the sigmoid relationship between propofol concentration and one of the Pd parameters (dPdTmax) in one volunteer. The results of Pd modeling are summarized in Tables 2 and 3. The observed weak differences in k_{e0}, EC_{50} of dPdTmax between ALINE and TFM failed to achieve statistical significance (p=0.07).

Fig. 1: Investigated pulse waveform parameters

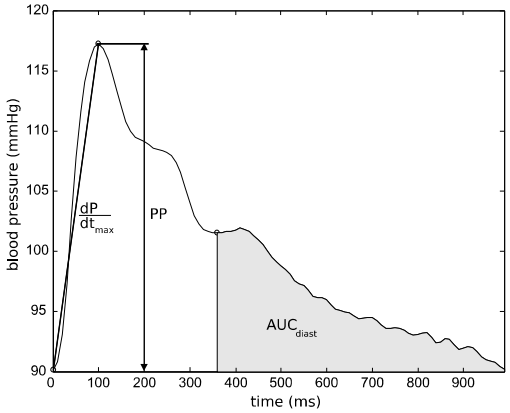
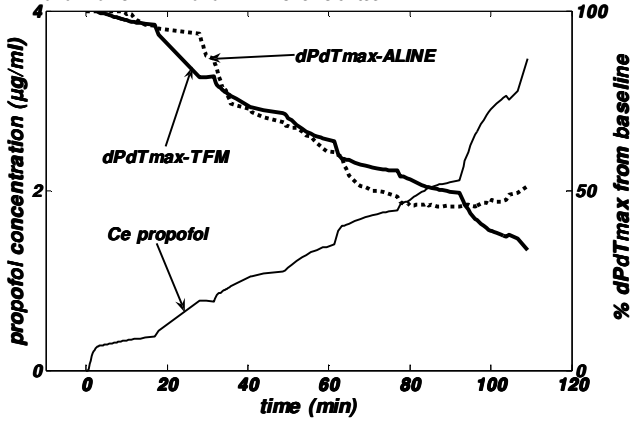


Fig. 2: Time course of propofol C_e and dPdTmax of ALINE and TFM in one volunteer



	ALINE		TFM	
	Baseline	**Minimum**	**Baseline**	**Minimum**
PP (mmHg)	74±9 (72)	51±7* (54)	41±10 (44)	24±7* (21)
dPdTmax (mmHg/s)	662±116 (608)	393±79* (400)	378±122 (424)	190±70* (162)
AUCdiast (mmHg·s)	8.3±1.4 (8.4)	4.2±1.3* (4.3)	4.9±1.3 (4.9)	2.1±0.8* (2.1)

Tab.1: Propofol induced changes on absolute values. * p<0.05 to baseline

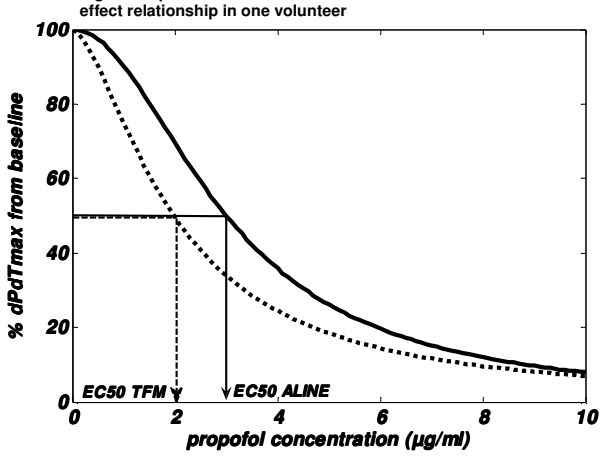
	ALINE		TFM	
	R (%)	**AR (%)**	**R (%)**	**AR (%)**
PP	-0.1±0.9 (0.3)	1.7±0.8 (1.6)	1.0±1.0 (0.9)	3.5±1.78 (3.3)
DPDTmax	-0.5±1.7 (-0.1)	2.5±1.3 (2.3)	0.5±2.2 (1.1)	3.6±1.8 (4.5)
AUCdiast	0.1±1.2 (0.2)	3.0±1.2 (3.2)	0.3±1.6 (-0.1)	4.8±1.8 (4.7)

Tab.2: Goodness of the pharmacodynamic fit

	ALINE			TFM		
	ke0 (1/min)	**EC50 (mmHg)**	**gamma**	**ke0 (1/min)**	**EC50 (mmHg)**	**gamma**
PP	0.22±0.26 (0.10)	2.5±1.7 (2.4)	0.8±0.4 (0.9)	0.15±0.13 (0.2)	2.0±1.8 (1.2)	1.6±1.2 1.3)
dPdTmax	0.11±0.13 (0.07)	3.7±2.1 (4.0)	1.2±0.8 (0.9)	0.22±0.07 (0.23)	1.7±1.5 (1.1)	1.4±1.2 (1.4)
AUCdiast	0.17±0.16 (0.12)	3.2±1.5 (3.3)	1.3±0.9 (1.1)	0.16±0.12 (0.12)	2.6±1.5 (2.2)	1.8±1.9 (1.5)

Tab.3: Pharmacodynamic parameters ke0, EC50, and gamma of sigmoid relationship propofol concentration - pulse waveform parameters PP, dPdTmax, and AUC diast

Fig. 3: Propofol concentration – dPdTmax effect relationship in one volunteer



Conclusion: Continuous non-invasive monitoring of pulse waveform parameters may be useful for pharmacodynamic studies on drug induced changes of pulse waveform and may add useful information to routine measurement of arterial blood pressure.

References:1. *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 5th edition*. 2005, Hodder Arnold: London.; **2** Hashimoto, J., Y. Imai, and M.F. O'Rourke, *Indices of pulse wave analysis are better predictors of left ventricular mass reduction than cuff pressure.* Am J Hypertens, 2007. 20(4): p. 378-84.; **3** Jeleazcov, C., et al. *Pharmacodynamic modelling of changes in arterial blood pressure during propofol anesthesia in volunteers: comparison between invasive and continuous noninvasive measurements*. WC 2009, *IFMBE Proceedings 25/VII*: 582-5.