The use of noninvasive continuous cardiac output to monitor the hemodynamic effects of propofol–fentanyl versus propofol–ketamine induction

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Background
Noninvasive continuous cardiac output monitoring method utilizing ECG and a pulse oximeter wave was based on hemodynamic analysis combined with pulse wave transit time. Propofol injection may induce a significant decrease in blood pressure. The use of ketamine with propofol may reduce the dose and the hemodynamic effect of propofol.

Patients and methods
Sixty female patients, ASA I and II, undergoing dilatation and curettage were divided into two equal groups. The first group received propofol (1 mg/kg) + fentanyl (1 μg/kg), whereas the second group received propofol (1 mg/kg) + ketamine (0.5 mg/kg) as induction agents. Continuous cardiac output monitoring was performed using pulse wave transit time technology. Hemodynamic data such as oxygen saturation through pulse oximetry, heart rate, and blood pressure were recorded every minute.

Results
Statistically significant differences between both groups were observed in diastolic, systolic, mean blood pressure, heart rate, and cardiac output. The propofol/fentanyl group showed a significant decrease in diastolic, systolic, and mean blood pressure, heart rate, and cardiac output compared with the propofol/ketamine group.

Conclusion
Noninvasive cardiac output measurement utilizing ECG, noninvasive blood pressure, and a pulse oximeter is a reliable method. Hemodynamic parameters including blood pressure, heart rate, cardiac output, and cardiac output index decreased with the induction of propofol and fentanyl combination, but were stable with the use of a propofol and ketamine combination.

Keywords:
fentanyl, ketamine, noninvasive cardiac output, propofol

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Introduction

The aim of hemodynamic monitoring is to maintain adequate tissue perfusion. It is necessary to monitor the cardiac output continuously to avoid hypoperfusion or fluid overload that can cause heart failure, especially in critical patients. Noninvasive continuous cardiac output monitoring method utilizing ECG and a pulse oximeter wave was based on hemodynamic analysis combined with pulse wave transit time (PWTT) [1].

Ketamine is an agent that has analgesic and amnestic properties. It protects airway reflexes and can be administered by multiple routes of administration, but it is associated with hemodynamic alterations, dysphoric emergence reactions, emesis, and a prolonged recovery period. Ketamine is also relatively contraindicated in patients with hypertension, increased intracranial pressure, ischemic heart diseases, or underlying neuropsychiatric comorbidities such as seizures or psychoses [2,3].

Propofol has been claimed to be the best available anesthetic drug because of its rapid smooth induction, short duration of action, and swift and clear recovery. The standard propofol dose of 2 mg/kg administered over the recommended time of 30 s for induction of anesthesia is associated with few disadvantages. Patients may experience pain during an injection of propofol; some patients show dystonic movements and in the majority of patients, there is a significant decrease in blood pressure on induction [4,5].

Ketofol (ketamine/propofol combination) was used for procedural sedation and analgesia. The opposing hemodynamic and respiratory effects of each drug may enhance the utility of this drug combination, increasing both safety and efficacy and enabling reduction in the dose of propofol required to achieve sedation [6].

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The aim of this study was to use noninvasive continuous cardiac output monitoring to compare the hemodynamic effects of induction with propofol–fentanyl versus propofol–ketamine.

Patients and methods

This comparative study was carried out at Misr University for Science and Technology Hospital. After obtaining patients' informed consent and ethical committee approval, 60 female patients, American Society of Anesthesiologist Physical Status (ASA) I and II, undergoing dilatation and curettage were divided into two groups of 30 patients each. Patients who had taken sedatives in the last 24 h, had neurological problems, cardiac, endocrinal diseases, or had been receiving treatment for psychiatric disorders, and those with a history of sensitivity to egg proteins, or pulmonary diseases were excluded from the study.

On arrival to the operating room, after patient orientation, an intravenous catheter was placed and physiological ringer's solution was infused at a rate of 4 ml/kg. ECG electrodes were placed, pulse oximetry was performed, and noninvasive blood pressure was determined. Noninvasively measured continuous cardiac output (estimated continuous cardiac output) is a new technology to determine the cardiac output using PWTT, which is obtained by pulse oximetry and ECG signals from each cycle of the ECG and peripheral pulse wave. The Nihon Kohden (Nishiochiai, Shinjuku-ku, Tokyo, 161-8560, Japan) (Life Scope) monitor was used to measure the previous parameters.

Hemodynamic data, oxygen saturation (SpO_2) by pulse oximetry, heart rate, blood pressure (diastolic, systolic, and mean), and cardiac output were recorded every minute, before the start of induction, and throughout the induction period till 10 min. The first group received propofol 1 mg/kg+fentanyl 1 μg/kg (PF group) and the second group received propofol 1 mg/kg+ketamine 0.5 mg/kg (PK group). Induction agents were administrated for 30 s intravenously. After 10 min and loss of verbal contact, all patients in both groups were maintained on anesthesia with 2% sevoflurane on an open mask.

During the study period, all patients received 100% O_2 4 l/min with a face mask through a circle system and no surgical stimulus was allowed. Adverse effects were recorded in both groups such as nausea, vomiting, vertigo, visual disturbances, and hemodynamic parameters (heart rates, mean blood pressure, and SpO_2 postoperatively).

Statistical methodology

Analysis of data was carried out by an IBM computer using statistical program for social science (SPSS statistical package, version 16, Chicago, Illionois, USA). Quantitative variables were described as mean ± SD. Qualitative variables were described as number and percentage. An unpaired *t*-test was used to compare quantitative variables in parametric data (SD <50% mean) and a paired *t*-test was used to compare quantitative variables within the same group. A *P* value more than 0.05 was considered nonsignificant, whereas *P* values less than 0.05 and 0.01 were considered significant and highly significant, respectively [7].

Results

The demographic data of patients in the PF and PK groups are reported in Table 1. No statistically significant differences were found between the two groups in age, weight, height, BMI, and body surface area.

The PK group showed a statistically significant decrease in heart rate and blood pressure (diastolic, systolic, and mean) compared with the PK group during induction time as shown in Figs. 1–3. In the PF group, there was a significant decrease in heart rate (the decrease started from the first minute till the eighth minute) and blood pressure (diastolic, systolic, and mean), but in the PK group, there was no significant change.

For SpO_2, there were no significant changes between the propofol/fentanyl and the PK group as well as within groups during the induction period as shown in Table 2.

Figure 4 shows the cardiac output and cardiac output index of PF and PK groups. There were highly statistically significant differences between PF and PK groups, where the PF group showed a significant decrease in cardiac output and cardiac output index starting at 2 till 10 min. In the PF group, there was a significant decrease in cardiac output and cardiac output index, but in the PK groups, there was no significant change during induction time.

Table 1 Comparison between propofol–fentanyl group/ketofol groups of general data

Variables	PF	PK	*t*	*P*
Age (years)	29.0 ± 6.0	31.7 ± 6.0	0.9	>0.05 (NS)
Weight (kg)	83.3 ± 8.0	85.0 ± 8.9	1.2	>0.05 (NS)
Height (cm)	165.9 ± 9.0	166.7 ± 5.8	0.9	>0.05 (NS)
BMI (kg/m^2)	30.5 ± 2.0	30.8 ± 2.1	0.4	>0.05 (NS)
BSA (m^2)	1.98 ± 0.4	1.97 ± 0.3	0.2	>0.05 (NS)

Results were expressed as mean ± SD; BSA, body surface area; NS, nonsignificant; PF, propofol 1 mg/kg+fentanyl 1 μg/kg; PK, propofol 1 mg/kg + ketamine 0.5 mg/kg.

The adverse effects of propofol/fentanyl and propofol/ketamine induction are presented in Table 3. Patients in the PF group had bradycardia (40%) and hypotension (70%). However, in the PK group, nausea, vomiting, and visual disturbances where recorded, representing 17, 3, and 2%, respectively.

Table 2 Comparison between propofol–fentanyl group/ketofol groups of SpO_2

Variables	PF	PK	*t*	*P*
SpO_2.0	98.0 ± 1.1	98.0 ± 1.1	0.2	>0.05 (NS)
SpO_2.1	98.0 ± 1.2	97.0 ± 1.3	0.4	>0.05 (NS)
SpO_2.2	98.0 ± 1.1	97.7 ± 1.5	0.8	>0.05 (NS)
SpO_2.3	97.8 ± 1.1	97.5 ± 1.3	0.2	>0.05 (NS)
SpO_2.4	98.0 ± 1.2	97.8 ± 1.2	0.7	>0.05 (NS)
SpO_2.5	98.0 ± 1.2	97.7 ± 1.3	0.6	>0.05 (NS)
SpO_2.6	98.0 ± 1.1	97.5 ± 1.2	0.7	>0.05 (NS)
SpO_2.7	97.8 ± 1.3	97.9 ± 1.2	0.11	>0.05 (NS)
SpO_2.8	98.0 ± 1.3	97.8 ± 1.2	0.14	>0.05 (NS)
SpO_2.9	98.0 ± 1.1	97.7 ± 1.1	0.9	>0.05 (NS)

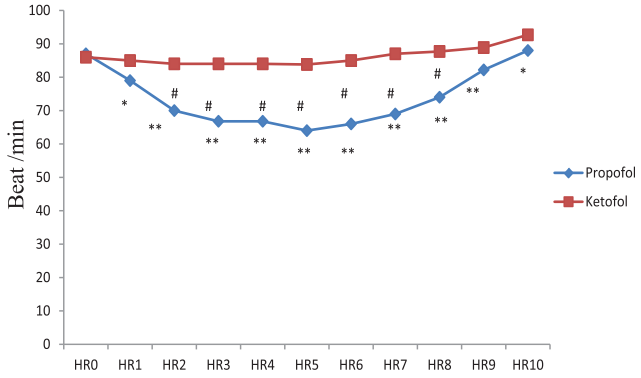
Results were expressed as mean ± SD; NS, nonsignificant; PF, propofol 1 mg/kg + fentanyl 1 μg/kg; PK, propofol 1 mg/kg + ketamine 0.5 mg/kg; SpO_2, oxygen saturation.

Table 3 Adverse effects of propofol–fentanyl/ketofol induction

Variables	PF	PK
Bradycardia	12 (40)	0 (0)
hypotension	21 (70)	0 (0)
SpO_2	0 (0)	0 (0)
Nausea	0 (0)	5 (17)
Vomiting	0 (0)	3 (10)
Visual disturbances	0 (0)	2 (7)

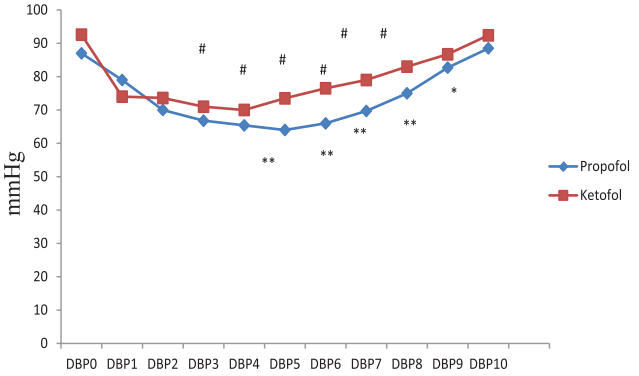
Results were expressed as *n* (%); PF, propofol 1 mg/kg +f entanyl 1 μg/kg; PK, propofol 1 mg/kg + ketamine 0.5 mg/kg; SpO_2, oxygen saturation.

Figure 1



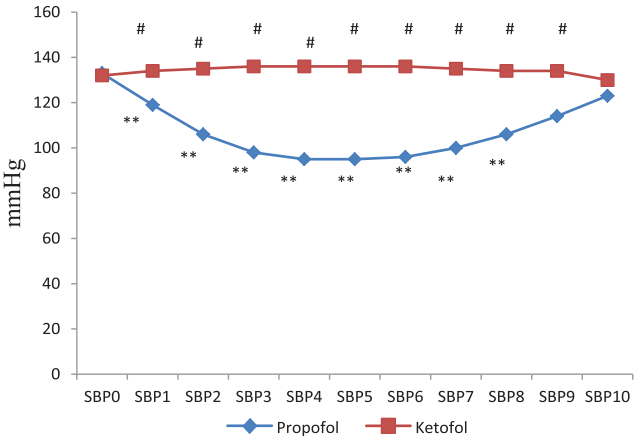
Changes in heart rate (HR) in the propofol–fentanyl/propofol–ketamine groups. HR0 = baseline. Results were expressed as mean ± SD. **Significant to baseline. #Significant between the propofol–fentanyl/propofol–ketamine groups.

Figure 2



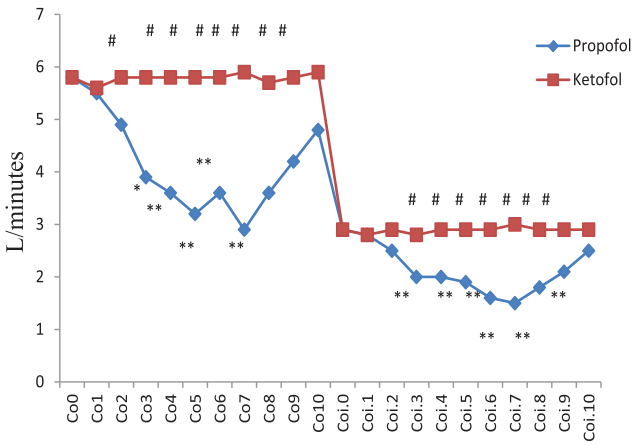
Changes in diastolic blood pressure (DBP) in the propofol–fentanyl/propofol–ketamine groups. DBP0 = baseline. Data expressed as mean ± SD. **Significant to baseline. #Significant between the propofol–fentanyl/propofol–ketamine groups.

Figure 3



Changes of systolic blood pressure (SBP) in the propofol–fentanyl/propofol–ketamine groups. SBP0 = baseline in Figure 3. Data expressed as mean ± SD. **Significant to baseline. #Significant between the propofol–fentanyl/propofol–ketamine groups.

Figure 4



Changes of cardiac output (CO) and cardiac output index (COI) in the propofol–fentanyl/propofol–ketamine groups. Data are expressed as mean ± SD. **Significant to baseline. #Significant between the propofol–fentanyl/propofol–ketamine groups.

Discussion

The decrease in blood pressure in patients remains a major problem during induction with propofol, especially in hypertensive patients, ischemic heart disease patients, and in those with cerebrovascular disease. Combining propofol with fentanyl produced a decrease in hemodynamic parameters such as heart rate, diastolic, systolic, mean blood pressure, and cardiac output as well as cardiac index in contrast to the combination of propofol and ketamine, which led to a lower decrease in hemodynamic parameters. Preliminary studies indicated that ketamine may be a useful alternative to opioid adjuncts during propofol sedation and that the sympathomimetic effects of ketamine may be effective in counteracting the hemodynamic depression of propofol [8].

Hypotension following induction with propofol has been considered to act by different mechanisms. Propofol may lead to a reduction in the systemic vascular resistance and cardiac output by less than 20% [5].

Propofol-induced hypotension is mediated by inhibition of the sympathetic nervous system and impairment of the baroreflex regulatory mechanism [9], venous smooth muscle relaxation leading to an increase in venous capacitance, which may contribute toward hypotension [10]. Propofol also exerts a negative inotropic effect on the heart and moderately depresses cardiac function (more than thiopentone and ketamine). On propofol induction, it resets the baroreceptor reflex, resulting in a reduction in blood pressure without increasing heart rate and a significant reduction in systemic vascular resistance, cardiac index, stroke volume (SV), and left ventricle stroke work index and also direct myocardial depression at doses above 0.75 mg/kg [11].

Ketamine is a phencyclidine derivative with dissociative, sedative, analgesic, and amnestic properties that preserves muscle tone and protects airway reflexes and spontaneous respiration. Pretreatment with ketamine has proved effective as it counteracts the hemodynamic depression of propofol and produces hemodynamic stability because it increases circulating catecholamine levels [12,13]. The cardiostimulatory effects of ketamine include increases in systemic and pulmonary arterial vascular resistance and pressure, heart rate, cardiac output, myocardial oxygen consumption, coronary blood flow, and cardiac work [14]. Ketamine induces significant increases in heart rate, mean arterial pressure, and plasma epinephrine levels. The sympathetic nervous system stimulation is centrally mediated. The hemodynamic stimulatory effect of ketamine depends on the presence of a robust myocardium and sympathetic reserve. In the absence of either, hypotension may result from myocardial depression.

Opioids have few direct effects on the heart. Fentanyl is associated with a vagus nerve-mediated bradycardia. The opioids do not depress cardiac contractility, provided they are administered alone; arterial blood pressure often decreases as a result of bradycardia and venodilatation [15,16].

Monitoring cardiac output is important for the management of patient circulation in an operation room or an intensive care unit. The change in PWTT obtained from an ECG and a pulse oximeter wave is correlated with the change in SV, from which cardiac output is derived [1].

A novel continuous cardiac output monitor is based on PWTT. PWTT obtained from an ECG and a pulse oximeter wave is correlated with the change in SV, from which cardiac output is derived. PWTT was calculated as the time from the ECG, R-wave peak to the rise point of the pulse oximeter wave. The rise point of the pulse wave was defined as the point at which the differentiated pulse wave reached 30% of its peak amplitude. PWTT was divided into three intervals: the pre-ejection period (PEP), PWTT through the elastic artery (T1), and PWTT through peripheral arteries (T2). PEP was defined as the time from the ECG R-wave to the rise point of the aortic root pressure wave. T1 was defined as the time from the rise point of the aortic pressure wave to the rise point of the radial artery pressure wave, and T2 was defined as the time from the rise point of the radial artery pressure wave to the rise point of the pulse oximeter wave in the fingertips. As PEP, T1, and T2 are included in PWTT [1] is obtained. PWTT = PEP + T1 + T2 [1].

Ishihara *et al.* [17] proved that changes in bias between estimated cardiac output and continuous cardiac output using a pulmonary artery catheter was less than 0.1 l/min, indicating the absence of any significant systematic error between the two measurements.

In terms of the effects of propofol/fentanyl on cardiac output, the results of the present study are consistent with those of Takizawa *et al.* [18] and Bennarosh *et al.* [19]. They reported a 17 to 35% decrease in cardiac output and cardiac index when they used a propofol and remifentanil combination in anesthesia.

In the present study, there were statistically significant differences between both groups (PF and PK) in heart rate as well as within-group PF, but not within-group PK. These results are comparable with those of the study by Zahoor and Ahmed [20], that there is a decrease in heart rate on propofol injection, and comparable with the study by Shah and Adaroja [21], that induction with propofol produces bradycardia. There were statistically

significant differences between both groups (PF and PK) in diastolic, systolic, and mean blood pressure as well as a statistically significant difference within-group PF. These results are in agreement with the results of Akin *et al.* [22], who found a reduction in diastolic, systolic, and mean blood pressure on administration of propofol. In another study of Akin *et al.* [23], the results were comparable with the present study, where blood pressure and heart rate were lower in the propofol group than in the ketofol group. Zahoor and Ahmed [20] studied the effect of propofol induction on blood pressure; they found a 15–20% decrease in systolic, diastolic, and mean blood pressure , which is similar to the results of the present study. Aouad *et al.* [24] found that significantly more children developed hypotension (63.6 vs. 23.4%) and bradycardia (48.5 vs. 23.4%) in the propofol group compared with the PK group; these results were consistent with the present study, where there was a significant decrease in blood pressure and heart rate in the PF group compared with the PK group.

Akin *et al.* [25] reported that the differences in SpO_2 values were similar in the two groups and hemodynamic data (systolic arterial blood pressure and heart rate) were not statistically significant, between both groups, and the both groups were propofol-fentanyl used in the first group and ketamine – propofol in the second group on induction of anesthesia. For SpO_2 values, the results were similar to those of the present study, but hemodynamic parameters as heart rate and blood pressure were different.

In terms of side effects, bradycardia occurred in 3% and hypotension in 2% of the patients in the PF group and nausea in 17%, vomiting in 10%, and visual disturbances in 7% of the patients in the PK group, which were not in agreement with the results observed by Akin and colleagues in their study, in which bradycardia occurred in 15% of the patients in the PF group and nausea in 7%, vomiting in 3%, and visual disturbances in 10% of the patients in the PK group. These differences may have been because of the limited numbers of patients in both researches [24].

Conclusion

Noninvasive cardiac output measurement utilizing ECG, noninvasive blood pressure, and SpO_2 is a reliable method. Hemodynamic parameters such as blood pressure, heart rate, cardiac output, and cardiac output index were decreased on induction with the combination of propofol and fentanyl, but stable on induction with the combination of propofol and ketamine.

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Conflicts of interest

There are no conflicts of interest.

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