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SEDATION AND RESPIRATORY MECHANICS IN MAN

A. GELB, P. SOUTHORN, K. REHDER AND E. P. DIDIER

SUMMARY

The effects of sedation with halothane, enflurane or midazolam on respiratory mechanics and lung volumes were studied in young healthy volunteers, in the supine position. Functional residual capacity increased with halothane sedation, but was unchanged with sedation produced by enflurane or midazolam. Sedation with halothane and enflurane, but not midazolam, tended to increase lung static recoil pressure. Total lung capacity was decreased during sedation with midazolam. No evidence was found that sedation with these three agents increased airway resistance. These findings imply that changes in respiratory mechanics induced by the residual effects of anaesthetic agents are unlikely to contribute significantly to the impairment in pulmonary gas exchange which may occur in the period immediately after operation.

In a study which examined four subjects lying supine while breathing subanaesthetic concentrations of halothane (0.2 minimal alveolar concentration (MAC)), three individuals decreased both their functional residual capacity (FRC) and the tonic muscle activity of the diaphragm and intercostal muscles (Muller et al., 1979). Sedation of recumbent subjects with diazepam 0.16–0.38 mg kg^{-1} has likewise been reported to decrease FRC (Prato and Knill, 1982). The present study used body plethysmography to determine whether a decrease in FRC and changes in pulmonary mechanics accompany sedation produced by enflurane, halothane or midazolam. If these changes occurred, they might contribute to hypoxaemia after operation, since the influences of sedative doses of anaesthetics persist for some time following general anaesthesia (Gelb and Knill, 1978).

SUBJECTS AND METHODS

Fifteen male and two female volunteers, having given their informed consent, participated in this study which was approved by this institution's human studies committee. They were studied first when awake and then sedated. Five volunteers were exposed to two levels of sedation with halothane (0.03 and 0.17 MAC) and six others to two levels of sedation with enflurane (0.04 and 0.16 MAC). Two of these 11 subjects were studied twice so that they could be exposed to both agents. The effect of sedation with midazolam was examined in the remaining six subjects.

The higher level of sedation with the two volatile agents had been found, in a pilot study, to be the maximum which would allow the co-operation of the subject in performing the respiratory manoeuvres. The first two subjects receiving midazolam were given an i.v. bolus of 0.12 mg kg^{-1} followed by a constant infusion of 0.025 mg kg^{-1} min^{-1} i.v. With this dose regimen, data collection had to be delayed until 50 min elapsed after the i.v. bolus, because the subjects were too sedated. To study the remaining four subjects receiving midazolam, the i.v. bolus dose was reduced to 0.09 mg kg^{-1} and the constant i.v. infusion increased to 0.05 mg kg^{-1} min^{-1}. With this dose, these four subjects were sedated but co-operative throughout the study.

The subjects fasted before the study and received no premedication. An oesophageal balloon (latex balloon 10 cm long, 3.5 cm perimeter) attached to an 80-cm polyethylene (PE-200) tube was positioned in the middle third of the oesophagus and its position was kept constant. The subject then lay supine in an Emerson tank respirator which had been modified to function as an air-conditioned volume displacement body plethysmograph (Westbrook et al., 1973). Its volume signal was accurate to 5% and frequency response flat to 8.5 Hz. The subject effected an air-tight seal with his lips around a mouthpiece, breathing room air through the latter, while the nostrils were occluded with a noseclip. The

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mouthpiece was connected via a 20-mm bore tubing to a calibrated heated pneumotachograph (Fleisch No. 3) positioned just outside the plethysmograph. An end-tidal gas sampler (Rahn et al., 1946) and a unidirectional J-valve were attached to the distal end of the pneumotachograph via a slide valve. This slide valve allowed removal of the relatively high resistance J-valve from the expiratory limb during the maximal expiratory flow-volume manoeuvre.

The oesophageal balloon was filled with 0.8 ml of air and this volume was confirmed repeatedly throughout the study. Pressure in this balloon (P_{oes}) and lateral airway pressure (P_{ao}) just outside the mouth were transduced using strain gauges (PM-131). Transpulmonary pressure (P_{tp}) was considered to equal the difference between P_{ao} and P_{oes}. The precise location of the oesophageal balloon was adjusted to a position in the oesophagus where tracheal artefacts were absent and cardiac artefacts minimal. Correct function of the balloon was confirmed throughout the study by ensuring that P_{tp} remained constant when the subject inspired and expired while the airway was momentarily occluded. All signals were recorded on a Honeywell 1612 Visicorder and on an Ampex FM eight-channel tape recorder. Arterial pressure, determined by arm-cuff, and heart rate were recorded every 5 min and the ECG was displayed continuously on an oscilloscope.

Measurements were performed in a set sequence. The subject's thoracic gas volume (V_{tg}) was quantified first. Measurement of V_{tg} permitted all other lung volumes to be related to absolute lung volume. From three reproducible V_{tg} and vital capacity measurements (within 5%), total lung capacity (TLC) and its subdivisions, including FRC, were calculated. V_{tg} was again measured and this was followed by 5 min of normal quiet breathing during which inspiratory and expiratory flows and transpulmonary pressure were recorded. Finally, the subject was required to produce three consistent static deflation pressure–volume (PV) curves, followed by three reproducible maximum expiratory flow–volume (FV) curves. Immediately before each PV and FV curve, V_{tg} was determined and the subject inspired maximally twice to ensure a similar volume history.

After completing these measurements, the subject was sedated either with the low concentration of halothane or enflurane vaporized in air or with midazolam. To achieve a stable level of sedation with the volatile agents before obtaining measurements, the subject inspired the anaesthetic for 20 min, taking frequent deep breaths during this period. The progress of equilibration was estimated by measurements of end-tidal concentrations of the volatile agent (gas chromatography) sampled 20 min after inspiration of the volatile anaesthetic commenced and again at the end of a set of measurements. From these two measurements of end-tidal anaesthetic concentrations, the values for the fractional MAC were calculated. After completing measurements while breathing the low concentration of volatile anaesthetic, the subject inhaled the greater concentration for 20 min and then repeated the above sequence of measurements.

To mitigate the artefact created by cardiogenic oscillations on transpulmonary pressure, oesophageal pressure measurements were standardized by making these measurements coincident with the P-wave of the simultaneously recorded ECG. V_{tg} was calculated from Boyle's Law (DuBois et al., 1956). Average pulmonary resistance (R_L) during quiet breathing was calculated by the isovolume method of Frank, Mead and Ferris (1957). The mean of 10 breaths is reported. Static lung compliance (Cst_L) was measured from the static deflation PV curves between 45 and 55% of the control TLC. Static lung elastic recoil pressure (Pst_L) was measured at 50% control TLC from the static deflation PV curves. The mean values from all subjects were subjected to a two-tailed paired t test to assess statistical significance.

RESULTS

The subject experienced no complications from the study. Because of excess sedation, the first two subjects receiving midazolam could not perform the measurement sequence until 50 min had elapsed following the start of administration of this drug. The data generated thereafter were included in the data analysis.

The average age, height and weight were 26 ± 1 (SD) yr, 1.79 ± 0.08 m, and 74 ± 19 kg for the enflurane group, 27 ± 1 yr, 1.78 ± 0.09 m, and 86 ± 19 kg for the halothane group, and 27 ± 2 yr, 1.80 ± 0.06 m and 83 ± 15 kg for the midazolam group. The mean MAC achieved for halothane and enflurane were similar (0.03 and 0.17 MAC for halothane and 0.04 and 0.16 MAC for enflurane). The mean ratios of the end-expired to inspired volatile anaesthetic concentration 20 min after the inspiration of volatile agents had commenced and at the completion of measurements at each level of sedation were 0.49 and 0.55 for 0.03 MAC

TABLE I. *Lung volumes.* **Different from control (paired t test) ($P < 0.05$)*

Variable (litre)	Enflurane ($n = 6$)		Halothane ($n = 5$)		Midazolam ($n = 6$)	
	MAC	Mean ± SEM	MAC	Mean ± SEM		Mean ± SEM
FRC	Control	2.42 ± 0.13	Control	2.19 ± 0.20	Control	2.45 ± 0.21
	0.04	2.41 ± 0.18	0.03	2.35 ± 0.21*		2.33 ± 0.14
	0.16	2.42 ± 0.16	0.17	2.44 ± 0.23*		
TLC	Control	6.98 ± 0.44	Control	7.14 ± 0.56	Control	7.40 ± 0.46
	0.04	7.03 ± 0.44	0.03	7.29 ± 0.56		7.13 ± 0.44*
	0.16	6.81 ± 0.42	0.17	7.30 ± 0.59		
RV	Control	1.66 ± 0.12	Control	1.59 ± 0.24	Control	1.69 ± 0.13
	0.04	1.60 ± 0.23	0.03	1.66 ± 0.22		1.67 ± 0.10
	0.16	1.65 ± 0.12	0.17	1.67 ± 0.27		

halothane, 0.56 and 0.69 for 0.17 MAC halothane, 0.60 and 0.76 for 0.04 MAC enflurane, and 0.67 and 0.78 for 0.16 MAC enflurane.

Lung volume (table I). Both levels of halothane sedation produced a consistent and significant ($P < 0.05$) increase in the subject's FRC. There was no consistent change in FRC with enflurane or midazolam sedation (fig. 1). Both subjects who were studied once with enflurane and once with halothane showed, at both concentrations, an increase in FRC with halothane but not with enflurane. Mean TLC decreased significantly

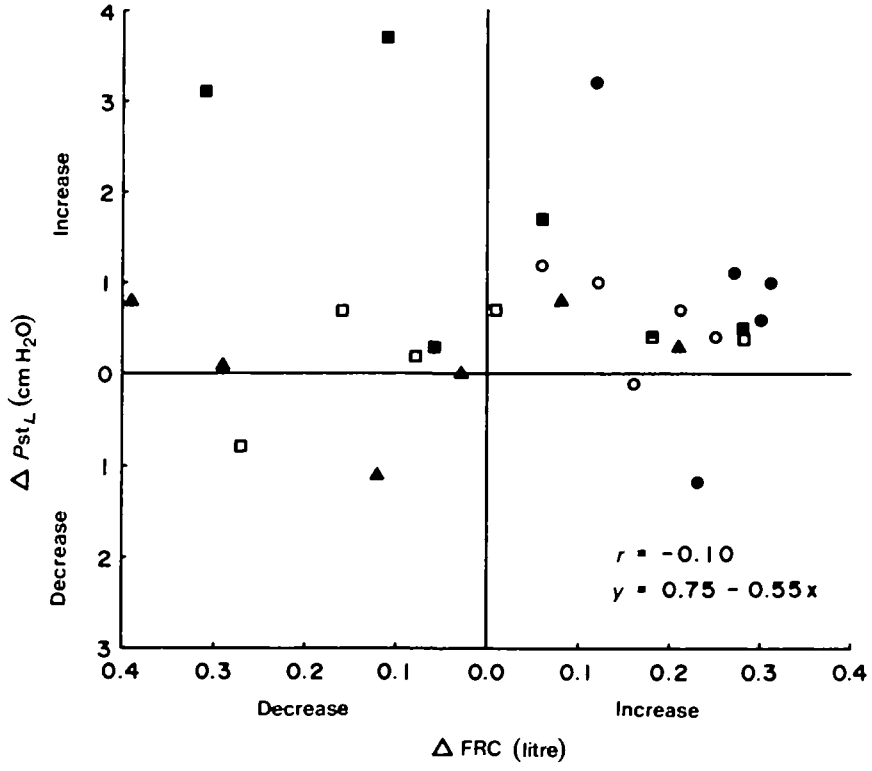

FIG. 1. Change in FRC with sedation: ○ = 0.03 MAC halothane; ● = 0.17 MAC halothane; □ = 0.04 MAC enflurane; ■ = 0.16 MAC enflurane; ▲ = midazolam. Note the consistent increase in FRC with halothane sedation. There was no correlation between change in elastic lung recoil pressure and change in FRC.

TABLE II. *Compliance and recoil pressure of lung. *Different from control (paired t test) ($P<0.05$)*

	Enflurane ($n=6$)		Halothane ($n=5$)		Midazolam ($n=6$)	
Variable	MAC	Mean ± SEM	MAC	Mean ± SEM		Mean ± SEM
C_{stL}	Control	0.27 ± 0.05	Control	0.28 ± 0.05	Control	0.21 ± 0.02
(litre	0.04	0.27 ± 0.05	0.03	0.27 ± 0.04		0.26 ± 0.03*
cmH_2O^{-1})	0.16	0.27 ± 0.03	0.17	0.27 ± 0.04		
P_{stL}	Control	−0.10 ± 1.0	Control	0.30 ± 0.4	Control	0.5 ± 0.7
(cm H_2O)	0.04	0.20 ± 1.0	0.03	1.00 ± 0.4*		0.6 ± 0.8
	0.16	1.60 ± 1.0*	0.17	1.30 ± 0.7		

($P<0.05$) with midazolam, but remained unchanged during sedation produced by halothane or enflurane. Residual volume (RV) did not change with sedation produced by any of the three agents.

Lung pressure–volume relationship (table II). Sedation with both enflurane and halothane tended to shift the PV curve to the right so that, at equivalent lung volumes, a greater pressure was required to keep the lungs inflated (fig. 2). At 50% of control TLC, the increase in P_{stL} was significant ($P<0.05$) with 0.16 MAC enflurane and 0.03 MAC halothane, but failed to reach significance with 0.04 MAC enflurane ($P=0.15$) and with 0.16 MAC halothane ($P=0.13$). No significant change in P_{stL} was observed with midazolam sedation. No significant correlation existed between the changes in FRC and P_{stL} (fig. 1). C_{stL} increased significantly ($P<0.05$) with midazolam sedation, but did not change significantly with sedation induced by enflurane or halothane.

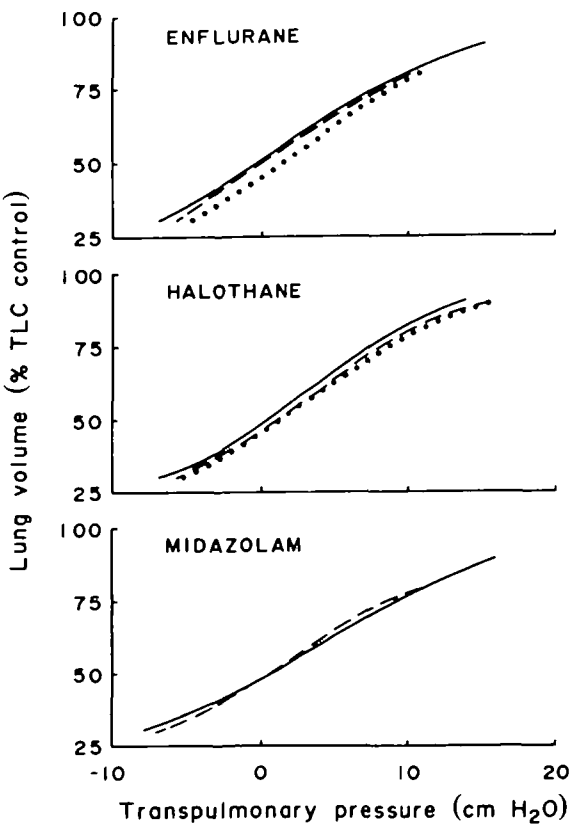

FIG. 2. Mean static lung pressure–volume curves. Top panel: control (——), low (---) and high (...) levels of enflurane sedation. Middle panel: control (——), low (---) and high (...) levels of halothane sedation. Bottom panel: control and midazolam sedation. Note enflurane and halothane, but not midazolam sedation, increased lung recoil pressure at all lung volumes.

Pulmonary resistance (table III). No statistically significant changes in R_L occurred during sedation with any of the three agents.

Flow-volume relationship (table III). Peak expiratory flow (PEF) was unchanged by sedation with halothane or enflurane, but decreased significantly ($P<0.05$) with that produced by midazolam. The maximum expiratory flow at 50% control TLC ($\dot{V}_{max}50\%$) did not change significantly with sedation produced by any agent.

DISCUSSION

The major findings of this study are that FRC was not significantly altered with enflurane or midazolam sedation, but increased consistently with halothane sedation; TLC was significantly decreased with midazolam sedation, but not altered by sedation with the other agents, and none of the agents studied changed R_L or $\dot{V}_{max}$ 50%.

Although the observed changes are small, they are of some interest. We believe the decrease in TLC with midazolam resulted from a loss of volition on the part of the subjects when sedated, although one might have expected an increase in RV to have occurred in this case. Peak expiratory flow is likewise affected by voluntary effort (Hyatt and Black,

TABLE III. *Pulmonary resistance, peak expiratory flow, and maximum expiratory flow at 50% control TLC. *Different from control (paired t test) ($P < 0.05$)*

	Enflurane ($n = 6$)		Halothane ($n = 5$)		Midazolam ($n = 6$)	
Variable	MAC	Mean ± SEM	MAC	Mean ± SEM		Mean ± SEM
R_L	Control	2.47 ± 0.25	Control	3.45 ± 0.49	Control	4.14 ± 0.25
($cm H_2O$	0.04	2.17 ± 0.33	0.03	3.09 ± 0.50		3.93 ± 0.79
litre s^{-1})	0.16	2.06 ± 0.27 ($n = 5$)	0.17	2.83 ± 0.28		
PEF	Control	8.65 ± 0.98	Control	8.18 ± 0.67	Control	10.14 ± 0.76
(litre s^{-1})	0.04	8.36 ± 0.80	0.03	8.50 ± 0.55		8.58 ± 0.58*
	0.16	8.11 ± 0.84	0.17	7.94 ± 0.51		
$\dot{V}_{max}50\%$	Control	3.30 ± 0.45	Control	3.27 ± 0.25	Control	3.08 ± 0.58
(litre s^{-1})	0.04	3.63 ± 0.40	0.03	3.27 ± 0.19		3.85 ± 0.45
	0.16	3.36 ± 0.36	0.17	3.20 ± 0.24		

1973), and lack of volition could also explain the significant reduction of peak expiratory flow with midazolam.

It is difficult to explain why our FRC results with halothane were opposite to those reported by Muller and co-workers (1979). The different methods used for measuring FRC between the two studies may have contributed to the different results—we used body plethysmography while Muller and colleagues used helium dilution and magnetometry. Body plethysmography measures thoracic gas volume, that is, communicating and trapped gas volumes, while helium dilution measures only the communicating gas volume.

We found a consistent increase in FRC with both levels of halothane sedation and both volunteers who were studied once with enflurane and once with halothane showed, at both concentrations, an increase in FRC with halothane but not with enflurane. It is well established that general anaesthesia is associated with a decrease in FRC. It appears possible that, at some point between the level of sedation we used and full anaesthesia, a decrease in FRC may occur. Muller and colleagues' (1979) four subjects were exposed to 0.20 MAC halothane, which was a slightly deeper level of sedation than we were able to achieve (0.17 MAC), so that some of their subjects may have been at the cross-over point associated with a reduction in FRC. To demonstrate such a cross-over, one must progressively increase the level of sedation until it occurs. Apparently the cross-over, if it occurs, occurs only after the loss of consciousness. It is therefore not possible to demonstrate it by any method dependent on the co-operation of the subject.

FRC is the lung volume at which the inward recoil of the lung is equal and opposite to the outward recoil of the chest wall. The increase in both FRC and lung recoil found during sedation with halothane would imply that there was a simultaneous and somewhat larger increase in outward chest-wall recoil. While is is generally accepted that general anaesthesia is associated with a decrease in skeletal muscle tone, stimulation before depression at the induction of anaesthesia with inhalation anaesthetics has been well documented (Gillespie, 1943). Indirect stimulation of human intercostal muscles *in vitro* was associated with "a marked positive inotropic effect which precedes the onset of muscle paralysis if the dosage of volatile agent is not too large" (Sabawala and Dillon, 1958). This initial augmentation of indirectly elicited twitches may be caused by alterations in the excitation–contraction coupling mechanism or in the contractile mechanism, or both (Waud and Waud, 1979). Such a stimulatory effect on inspiratory muscle tone could cause the increase in FRC.

Another possible reason for this discrepancy in effect on FRC between halothane *v.* enflurane and midazolam may relate to the subjects' being exposed to different levels of sedation with the three drugs. Although the MAC values of halothane and enflurane studied were similar, equal MAC fractions may not represent equivalent depths of sedation, since the MAC value represents only one point of a dose–response curve (Waud and Waud, 1970).

It has been suggested that the decrease in FRC occurring after the induction of anaesthesia is responsible for the associated changes in lung compliance and elastic recoil pressure (Rehder, 1979).

This hypothesis is supported by the observation that chest restriction in healthy awake individuals also causes a decrease in FRC and this is associated with a decrease in lung compliance and an increase in its recoil (Stubbs and Hyatt, 1972). The latter investigators hypothesized that these changes in compliance and recoil were caused by a decreased lung volume altering the properties of lung surfactant. We found a small but statistically significant increase in lung recoil pressure with halothane and enflurane without an associated decrease in FRC. This small increase in recoil pressure may result from a direct effect of enflurane and halothane on lung surfactant material. In dogs, general anaesthetics do have a small effect on lung-surface forces (Woo et al., 1970). During anaesthesia, this small direct effect may be overshadowed by a larger indirect effect consequent upon the reduction of lung volume.

In summary, sedation with halothane (0.03 and 0.17 MAC), enflurane (0.04 and 0.16 MAC), or midazolam resulted in small but statistically significant changes in pulmonary mechanics. These changes are probably of little or no clinical significance. Thus, it is unlikely that such sedation is responsible for the decrease in FRC and associated increase in the alveolar–arterial oxygen tension difference found in the period immediately after operation (Alexander et al., 1973).

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SEDATION ET MECANIQUE VENTILATOIRE CHEZ L'HOMME

RESUME

Nous avons étudié les effets de la sédation à l'halothane, à l'enflurane ou au midazolam sur la mécanique ventilatoire et les volumes pulmonaires de jeunes volontaires, en bonne santé, en décubitus dorsal. La capacité résiduelle fonctionnelle augmentait avec la sédation à l'halothane, mais n'était pas modifiée par la sédation à l'enflurane ou au midazolam. La capacité pulmonaire totale diminuait avec la sédation au midazolam. Il n'a pas été trouvé d'arguments pour dire que la sédation avec ces trois agents augmentait la résistance des voies aériennes. Ces résultats impliquent que les modifications de la mécanique ventilatoire induites par les effets résiduels des agents anesthésiques ont peu de chance de contribuer significativement aux altérations des échanges gazeux pulmonaires qui peuvent survenir au décours d'une intervention chirurgicale.

SEDIERUNG UND ATEMMECHANIK BEIM MENSCHEN

ZUSAMMENFASSUNG

Bei jungen gesunden Probanden wurde in liegender Position die Sedierungswirkung von Halothan, Enflurane oder Midazolam auf Atemmechanismen und Lungenvolumina studiert. Unter Halothansedierung vergrößerte sich die funktionnelle Residualkapazität, blieb jedoch bei Enflurane- oder Midazolamsedierung unverändert. Sedierung mit Halothan und Enflurane, nicht jedoch mit Midazolam, neigte dazu, die statische Compliance zu erniedrigen. Während Sedierung mit Midazolam war die totale Lungenkapazität erniedrigt. Es fand sich kein Hinweis dafür, daß die Sedierung mit einem der drei Wirkstoffe den Widerstand in den Atemwegen erhöhte. Die Ergebnisse lassen darauf schließen, daß Veränderungen in der Atemmechanik durch Hangover-Effekte von Anästhetika wahrscheinlich nicht signifikant zu einer Beeinträchtigung des Gasaustausches in der Lunge führen, wie sie in der unmittelbaren postoperativen Phase auftreten kann.

MECANISMOS RESPIRATORIOS Y SEDATIVOS EN EL HOMBRE

SUMARIO

Se estudiaron los efectos de la sedación con halotano, enflurano o midazolam en los mecanismos respiratorios y en los volúmenes pulmonares de jóvenes voluntarios sanos colocados en posición de tendido supino. La capacidad residual de carácter funcional aumentó con la sedación de halotano pero no varió en lo absoluto por la sedación producida por enflurano o midazolam. La sedación con halotano y enflurano, pero no con midazolam, tendió a incrementar la presión estática de retroceso de los pulmones. La capacidad pulmonar total disminuyó durante la sedación con midazolam. No se observó evidencia alguna de que la sedación con estos tres agentes aumentara la resistencia del conducto de aire. Estas observaciones implican que los combios en los mecanismos respiratorios inducidos por los efectos residuales de los agentes analgésicos difícilmente contribuirán de forma significativa al entorpecimiento del intercambio del gas pulmonar que puede tener lugar durante el periodo que sigue justo después de la operación.