## Clinical Evaluation of Isoflurane

# CARDIAC ARRHYTHMIAS

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PREVIOUS STUDIES OF cardiac arrhythmias during operation have not only shown the ubiquitous nature of such events, but have demonstrated that many factors contribute to their development.[19,23] Our purpose in this study of cardiac arrhythmias during isoflurane anaesthesia was to catalogue arrhythmias which occur, to identify the contribution of isoflurane (if any) to these arrhythmias, and to identify factors which correlated with an increased incidence of arrhythmias.

## MATERIALS AND METHODS

The demographic characteristics of the study population have been described in a previous section. Electrocardiographic monitoring was not a prerequisite for inclusion in this study, so only about 75 per cent of the patients had such monitoring during operation. The statistical analysis of cardiac arrhythmias during operation was restricted, however, to the monitored group, to ensure diagnostic accuracy.

Electrocardiographic monitoring during operation was done by routine techniques. Continuous recordings were not made, and no postoperative analysis of recordings was undertaken. Atrial, nodal, and ventricular arrhythmias were recorded during each of three periods: preoperative, the first 10 minutes of anaesthesia (induction) and after 10 minutes (maintenance). The occurrence of an arrhythmia was recorded without quantification of its frequency or haemodynamic significance.

Table 35 summarizes the variables which were analyzed for possible association with changes in the incidence of arrhythmias, and lists the comparison groups used for each analysis. Tests by chi square were used throughout. The analysis was identical for each type of cardiac arrhythmia (atrial, nodal, or ventricular) but not for each period. Because of the overwhelming influence of preoperative arrhythmias on their occurrence during operation most analyses were done on two subgroups of patients: those with arrhythmias preoperatively, and those without them. Every patient included in the study underwent at least one surgical procedure; however, many patients received no medications and had no organ system disease. These patients formed a control group for analysis of arrhythmia against the factors of current medications and organ system disease. Similarly, patients in whom there was no other intervention (e.g. no tracheal intubation) were used as the control group for the analysis of the effect of such interventions. In other cases, where no control group was available (e.g. the influence of procedure site on the incidence of arrhythmias), the comparison was made between the test group (e.g. intracranial surgery) and the rest of the population.

Since many comparisons were made between subgroups of the same data, the risk of incorrectly rejecting the null hypothesis (Type I or false positive error) was an important statistical consideration. Several techniques are available for reducing the chance of Type I errors, but each results in some increase in the chance of Type II (false negative) errors. (See the section on statistical methods for details). Despite the large data base used, many of the specific subgroups, such as patients with both circulatory and respiratory disease, were relatively small. The precision of the analysis of infrequent events such as arrhythmias is therefore limited.

The solution involved adjustment of the acceptable P-value for statistical significance by a factor related to the number of times each independent outcome (i.e. arrhythmia) was challenged in a statistical test. Each arrhythmia during each period (preoperative, induction, and maintenance) was analyzed for increased incidence with about 50 different variables. Accordingly, the P-value for statistical significance was reduced from 0.05 to 0.001 for significance tests by chi square. This resulted in exclusion of some variables which were marginally correlated with increased incidence of arrhythmias on previous sequential analysis. The clinical importance of these excluded associations was likely small. Thus the failure to

TABLE 35

SUMMARY OF VARIABLES ANALYZED AND CONTROL GROUPS FOR ANALYSIS OF VARIABLES.†

| Variable | Analysis | Comparison Group |
|---|---|---|
| Age | * | <50 years |
| ASA status | */+ | RP |
| Disease area | * | CG |
| Procedure site | | RP |
| Current medications | */preop arrhythmia | CG |
| Smokers | preop arrhythmia | Nonsmokers |
| Epinephrine | + | No epinephrine |
| Max isoflurane concentration | + | RP |
| Ave isoflurane concentration | + | RP |
| Preop pulse | preop arrhythmia | RP |
| Preop blood press. | preop arrhythmia | RP |
| Pulse (abs. & rel. chg) | + | RP |
| Blood press. (abs. & rel. chg) | + | RP |
| Nitrous oxide | + | No nitrous oxide |
| Adjuvant drugs | + | No adjuvants |
| Tracheal intubation | + | Not intubated |
| Controlled vent. | + | Spontaneous breathing |
| Muscle relaxant | + | No relaxants |

†The analysis was identical for each arrhythmia (atrial, nodal and ventricular) but differed among periods (preoperative, induction and maintenance).

*Analysis performed for each type of arrhythmia (atrial, nodal, ventricular) during each period (preoperative, induction, maintenance).

+Analysis performed for each type of arrhythmia during induction or maintenance, analyzed by subgroups with and without preoperative arrhythmias.

RP: each group was compared to the remainder of the population by chi-square.

CG: each group was compared to the control group – no disease, no current medications.

confirm such a relationship on the subsequent analysis was considered acceptable to avoid spurious associations which could be induced by repeated analysis of the same outcome against many variables.

Many factors such as age, ASA status, disease, and preoperative pulse rate and blood pressure may interact to alter the incidence of arrhythmias. Stepwise logistic regression analysis was used to differentiate the influence of these different variables on the incidence of arrhythmias.

## RESULTS

### *Artrial arrhythmias*

The overall incidence of atrial arrhythmias was low, being 3.6 per cent on induction and 3.9 per cent during maintenance. Preoperative atrial arrhythmias were present in 2.9 per cent of patients; however these patients accounted for a disproportionately large number of the arrhythmias observed during operation. Fifty-nine per cent of all atrial arrhythmias on induction and 53 per cent of all atrial arrhythmias during maintenance occurred in patients with atrial arrhythmias preoperatively.

The presence of preoperative atrial arrhythmias correlated significantly with age, ASA status, procedure site, current medications, and diseases present. Figure 5 shows that preoperative arrhythmias increased with age, being low until the fifth decade and rising rapidly thereafter. The increased incidence of arrhythmias in patients with circulatory disease (6.3 per cent $P < 0.0001$) is not surprising, since many types of circulatory disease are characterized by atrial arrhythmias. Over 75 per cent of the patients with multisystem disease had circulatory disease as well and, accordingly, multisystem disease was associated with a comparable incidence of atrial arrhythmias (7.3 per cent, $P < 0.00001$). The use of digitalis or diuretics by non-smokers increased the respective incidences of preoperative atrial arrhythmias to 16 per cent ($P < 0.00001$) and 5.7 per cent ($P < 0.001$) of the patients receiving these drugs. The control group (no medications, no organ system disease) had a 0.9 per cent incidence of atrial arrhythmias, significantly lower than that of the remainder of

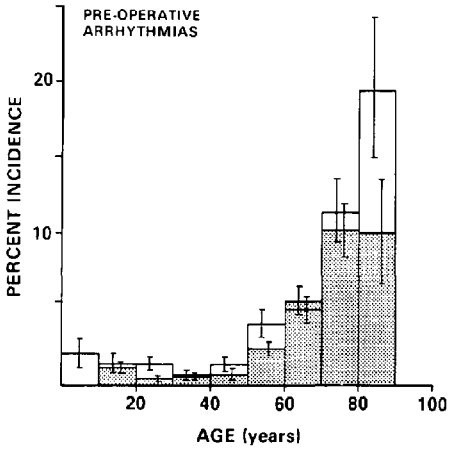


FIGURE 5 The mean ± 1 SD (percent all patients) with preoperative atrial (open bars) or ventricular (hatched bars) arrhythmias plotted for each decade.

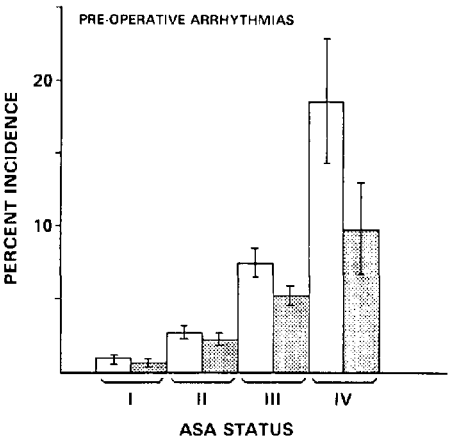


FIGURE 6 The mean ± 1 SD incidence (percent all patients) with preoperative atrial (open bars) or ventricular (hatched bars) arrhythmias plotted for each ASA status category.

the population ($P < 0.0001$). ASA status takes account of many aspects of disease and its severity. There was an increased incidence of preoperative atrial arrhythmias in patients with higher ASA status (Figure 6). There was also a high incidence of preoperative atrial arrhythmia in patients undergoing major vascular or open heart surgery, (9.0 [$P < 0.001$] and 18.5 [$P < 0.00001$], per cent respectively).

Preoperative atrial arrhythmias frequently persisted during induction and maintenance of anaesthesia. The incidence of these persistent arrhythmias was 77 per cent during induction. During maintenance the incidence was 72 per cent, but the difference between these two values was not significant. The small number of patients with preoperative atrial arrhythmias precluded other factors being postively associated with an increased incidence of atrial arrhythmias during induction or maintenance of anaesthesia.

Patients without preoperative atrial arrhythmias who were receiving digitalis therapy had in increased incidence of atrial arrhythmias on induction (9.1 per cent $P < 0.0001$) compared to the control group (0.7 per cent). New atrial arrhythmias on induction also occurred in 3.8 per cent of the patients having blood pressures over 20 kPa (150 torr) during induction ($P < 0.0001$). These patients had a mean age of 57.6 years and mean preoperative blood pressures of 23.9 kPa (180 torr).

In patients without preoperative atrial arrhythmias, an increased incidence of new atrial arrhythmias was observed during maintenance under several circumstances. Cardiac surgery was associated with the occurrence of a new arrhythmia in 13.6 per cent of the cases ($P < 0.00001$). New atrial arrhythmias occurred in 9.1 per cent of patients receiving digitalis glycosides ($P < 0.0001$) and preoperative bradycardia (pulse below 60 beats/minute) was associated with a 5.0 per cent incidence of new atrial arrhythmias ($P < 0.0001$). A notably higher percentage of patients receiving narcotics during operation (5.5 per cent) showed new atrial arrhythmias ($P < 0.0001$). Intraoperative tachycardia at rates over 150 beats/min was identified as an arrhythmia in 6.2 per cent of cases ($P < 0.00001$). Increasing blood pressure was also correlated with increasing incidences of atrial arrhythmias, as shown in Figure 7. Finally, the use of controlled ventilation correlated with an increased incidence of atrial arrhythmias (2.9 per cent, $P < 0.001$), while the incidence of new arrhythmias in intubated patients (2.5 per cent) fell just short of the level of statistical significance necessary for minimizing false positive errors ($0.005 > P > 0.001$).

Stepwise logistic regression demonstrated the overwhelming influence of preoperative arrhythmias on the incidence of arrhythmias during operation, producing a singular matrix when analysis of the other factors was attempted. Among the factors examined as predictors of arrhythmia on induction, the presence of circulatory disease and the age of the patient were the

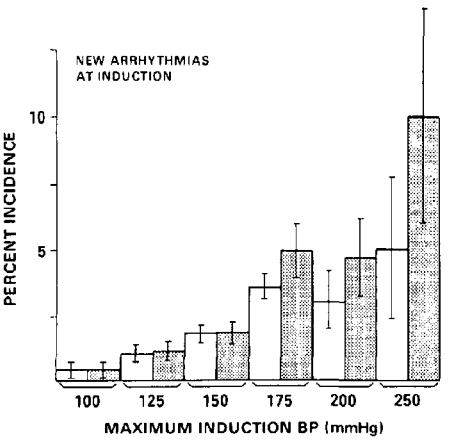


FIGURE 7 Mean ±1 SD incidence (percent all patients) for new atrial (open bars) or new ventricular (hatched bars) arrhythmias occurring at induction (1st 10 min of anaesthesia) plotted against the maximum blood pressure (mmHg) recorded during induction.

most important. ASA status, presence of preoperative ventricular arrhythmias and of nodal arrhythmias did not substantially alter the frequency in the predictive value of the model. The inclusion tended to reduce the magnitude of the circulatory disease coefficient, but did not substantially alter the coefficient associated with increasing age. Preoperative pulse rate, blood pressure and other preinduction arrhythmias proved to be of no predictive value in the model.

A similar analysis for atrial arrhythmias during maintenance revealed a somewhat different result. The presence of preoperative atrial arrhythmias again proved to be an excellent predictor of atrial arrhythmia during operation, with a smaller contribution to the prediction being made by the presence of circulatory disease. Unlike the model for induction arrhythmias, age was not a useful predictor of preoperative arrhythmias during maintenance, but ASA status was. Other factors included preoperative pulse rate and blood pressure, and preoperative nodal or ventricular arrhythmias again did not contribute to the model.

*Nodal arrhythmias*

Nodal arrhythmia was an infrequent event during the study. Only 55 of the 3,695 monitored patients (1.5 per cent) had nodal arrhythmias on induction, and 22 per cent of these occurred in subjects having preoperative nodal arrhythmias ($P < 0.00001$). During maintenance, a somewhat higher incidence of nodal arrhythmia was observed (2.1 per cent), with only 10 per cent of these arrhythmias occurring in patients who had a nodal arrhythmia preoperatively ($P < 0.00001$). There was a high incidence of nodal arrhythmias during both induction (63 per cent) and maintenance (47 per cent) in the 19 patients who had nodal arrhythmias preoperatively. Only the use of anticholinergics during operation correlated with an increased incidence of nodal arrhythmias during maintenance ($P < 0.00001$). No correlation with increased incidence of nodal arrhythmias during induction was identified.

*Ventricular arrhythmias*

The overall incidence of ventricular arrhythmias was low, being 2.5 per cent during induction and 2.3 per cent during maintenance. Preoperative ventricular arrhythmias were present in 1.9 per cent of the population, and these patients accounted for 33 per cent of all ventricular arrhythmias on induction and 35 per cent of such arrhythmias during the maintenance of anaesthesia.

An increased incidence of preoperative ventricular arrhythmias was associated with increasing age, ASA status, disease of certain organ systems, some operative sites and some current medications. The effect of age, shown in Figure 5, is simlar to the effect of age on atrial arrhythmias. There is a rapid increase in the incidence of arrhythmias after age 50. The incidence of preoperative ventricular arrhythmias was also positively correlated with ASA status (Figure 6). Patients with disease of the circulatory system or multisystem disease had a significantly increased incidence of ventricular arrhythmias 4.5 ($P < 0.0001$) and 5.8 ($P < 0.00001$) per cent respectively. Smokers receiving digitalis had an increased incidence of preoperative arrhythmias (31 per cent, $P < 0.0001$), as did nonsmokers receiving diuretics (4.7 per cent, $P < 0.0001$) or nitrates (16.4 per cent, $P < 0.0001$). Overall there was no difference in the arrhythmia rate between smokers and nonsmokers, and the numbers of patients in some of the individual subgroups was sufficiently small to question the general applicability of the results even though the criteria for statistical significance were met. For example, there were only 13 smokers who were receiving only digitalis therapy, and the four of those who had arrhythmias accounted for the association of digitalis, smoking and arrhythmias noted above.

In patients with preoperative ventricular ar-

rhythmias, the arrhythmia frequently recurred during induction (46 per cent of cases) and maintenance (44 per cent of cases). While the incidence of arrhythmia during induction did not correlate with ASA status in these patients, a strong positive correlation was noted between ASA status and the recurrence of ventricular arrhythmias during maintenance in these patients (Figure 8). The small number of subjects with preoperative ventricular arrhythmias made further statistical analysis of this subgroup inappropriate.

In patients without preoperative ventricular arrhythmias, new ventricular arrhythmias occurred during induction at a low rate (2.2 per cent). Only hypertension on induction was associated with a significantly increased incidence of arrhythmias, and then only at systolic pressures over 20 kPa (150 torr) (Figure 7). During maintenance, however, several factors were associated with an increased incidence of ventricular arrhythmia. Operations on the heart or major vessels were associated with an increased incidence of ventricular arrhythmias ranging from 6.3 per cent in vascular cases ($P < 0.001$) to 18 per cent in coronary artery surgery ($P < 0.00001$). The use of nitrates and beta blockers was associated with an 11.1 per cent incidence of new ventricular arrhythmias during operation ($P < 0.00001$).

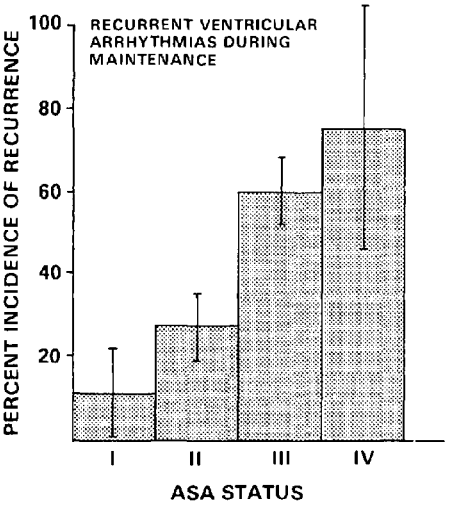


FIGURE 8 Mean ±1 SD incidence (percent all patients) for recurrent ventricular arrhythmias (present preoperatively) during maintenance plotted for each ASA status category.

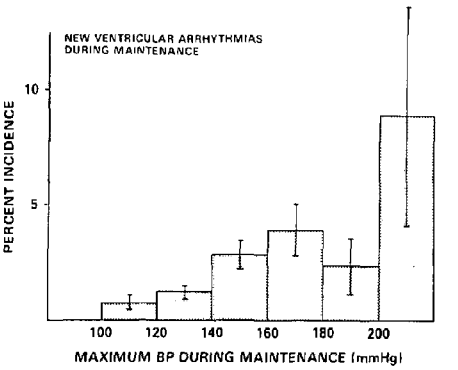


FIGURE 9 Mean ±1 SD incidence (percent all patients) for new ventricular arrhythmias occurring during maintenance plotted against the maximum blood pressure (mmHg) recorded during maintenance.

As with atrial arrhythmias, stepwise logistic regression analysis was done to identify factors contributing to the occurrence of ventricular arrhythmias during the induction and maintenance of anaesthesia. The models for ventricular arrhythmias during induction and maintenance were quite similar, showing the predominating factors to be the presence of a preoperative ventricular arrhythmia, age, and the presence of circulatory disease. No other factors, including preoperative blood pressure and pulse rate, presence of other preoperative arrhythmias or ASA status, made significant improvements to the accuracy of the model, although maximum blood pressure during maintenance was related (Figure 9).

## DISCUSSION

The overall incidence of arrhythmias observed in this study was quite low compared with studies of other agents when similar monitoring techniques were used.[19] The rates for arrhythmias during operation among patients who had them preoperatively are comparable, however, to the results from other studies.[22]

Factors associated with an increased incidence of atrial arrhythmias may be explained on the basis of patient factors and the stress of anaesthesia and surgery on the autonomic and circulatory systems. The presence of a preoperative atrial arrhythmia, increased age, and the presence of circulatory disease would all be expected to increase the incidence of atrial arrhythmias, and they did. Similarly, the asso-

ciation of atrial arrhythmias with procedures which involve manipulation of the heart or great vessels is hardly surprising. Furthermore, almost all of these patients had circulatory disease, which is widely known to be associated with a higher incidence of atrial arrhythmias. The increased incidence of new atrial arrhythmias in patients taking digitalis glycosides could be explained by the fact that they were older, had circulatory disease, had higher ASA status or required operations on the heart or great vessels.

Hypertension during induction and maintenance was associated with atrial arrhythmias. Light anaesthesia is known to produce sympathetic stimulation which, in turn, can result in atrial arrhythmias. Despite the fact that heart rate increased at induction, no other data were available to indicate a sympathomimetic effect as a result of light anaesthesia with isoflurane. The correlation of atrial arrhythmias and hypertension likely represents a purely statistical relationship of doubtful clinical significance, since both atrial arrhythmias and hypertension were associated with circulatory system disease.

The incidence of arrhythmias in patients receiving controlled ventilation represents an interesting problem. First, there is no a priori reason why controlled ventilation should produced arrhythmias. Other studies[23,25,26] have shown just the reverse – that decreased ectopy is present during controlled ventilation because hypercarbia is prevented. Second, the incidence of new arrhythmias in the patients with controlled ventilation (2.8 per cent) was not high, but appears so only because the incidence of arrhythmias in spontaneously breathing patients was even lower at 1.0 per cent. This lower rate of arrhythmias in spontaneously breathing patients was similar to the incidence of arrhythmia in the patients without significant disease and taking no medications (the control group). In addition, some procedures which had elevated rates of arrhythmias associated with them demand the use of controlled ventilation during operation. The distribution of age, ASA status, disease and procedures differed between the controlled ventilation and spontaneously breathing groups, and could explain the difference in the observed incidence of arrhythmias in the two groups. Regardless of its aetiology, the difference in the incidence of arrhythmias in these two groups is not of major clinical significance.

Nodal arrhythmias occurred infrequently under isoflurane anaesthesia. No associations were found with any of the factors examined except the occurrence of such arrhythmias preoperatively. The possible association between anticholinergics and nodal arrhythmias could be of clinical importance. Unfortunately, data on the temporal relationship of the arrhythmia and the anticholinergic use was not obtained.

Interestingly, many factors associated with increased rates of atrial arrhythmias were also associated with increased incidence of both types of ventricular arrhythmias, suggesting a common aetiological mechanism. Age, preoperative arrhythmias and diseases of the circulatory system were all associated with increased incidence of arrhythmias. Increasing age may simply correspond to the development of subclinical disease, while preoperative arrhythmias and circulatory disease would be expected to be associated with ventricular arrhythmias. The increased incidence of ventricular arrhythmias in smokers taking digitalis and in nonsmokers taking diuretics or nitrates may represent a biased distribution of patients with underlying circulatory disease and differing ages between the groups. Alternatively, diuretic-induced hypokalaemia could explain the increased incidence of arrhythmias in patients receiving those drugs and other studies have documented an increased incidence of ventricular arrhythmias in patients receiving digitalis.[20] No interaction between isoflurane and these agents need be postulated to explain the results observed.

As with atrial arrhythmias, hypertension was frequently associated with ventricular arrhythmias. The effect of hypertension on increasing ventricular myocardial oxygen consumption and the appearance of ventricular ectopy as a sign of inadequate myocardial oxygenation suggests that a causal relationship between hypertension and ventricular arrhythmias may exist. This hypothesis is further supported by the increased incidence of arrhythmia seen in patients taking nitrates and beta blockers (presumably for ischaemic heart disease). Hypertension may also be a sign of endogenous catecholamine release associated with light anaesthesia, and this may precipitate ventricular arrhythmias. Studies with other agents[24] have also demonstrated such an associated between hypertension and ventricular arrhythmias, presumably on the same basis.

The relationship between the use of nitrous oxide and ventricular arrhythmias, and between intraoperative barbiturates and ventricular arrhythmias represent two more interesting problems. Certainly there is no logical reason to expect that isoflurane/oxygen anaesthesia should

result in a higher incidence of arrhythmias during maintenance, unless these cases represent mostly cardiac surgery and procedures performed in patients too ill to tolerate normal inspired oxygen tensions. However, the present study did not confirm that such a biased population was present. In the case of the association with barbiturates, the situation is quite analogous to the association of nodal arrhythmias and anticholinergics, where the drug may have been given in response to the occurrence of the arrhythmia or the arrhythmia may have resulted from use of the drug. However, since no such relationship was seen during induction, when nearly 75 per cent of the patients received barbiturates, the production of ventricular ectopy by barbiturates seems most unlikely. Accordingly the more reasonable explanation is that barbiturates were administered to some patients in an attempt to deepen anaesthesia when ventricular ectopy suggested inadequate depth of anaesthesia.

The failure to demonstrate significant effects of most of the factors discussed above on the incidence of arrhythmias is not surprising; however, the lack of statistical significance for the incidence of arrhythmia when epinephrine was administered was somewhat unexpected. Since exogenous epinephrine can produce ventricular arrhythmias in the absence of anaesthesia, one might have expected to find an increased incidence of arrhythmias in patients receiving epinephine during operation. However, only two per cent of the subjects received epinephrine, and the incidence of arrhythmias in this group was too low to be statistically different from the overall incidence of arrhythmias.

In summary, this study of cardiac arrhythmias during isoflurane anaesthesia demonstrated that many factors were correlated with increased incidence of arrhythmias. In none of the extensive analyses did isoflurane itself appear to be a factor associated with development of arrhythmias. This study thus confirms both earlier clinical experience and laboratory studies which reported stability of the cardiac rhythm under isoflurane anaesthesia.