have submitted. It is a striking graphic confirmation of the observation reported by us and others, ie, that catheters in the right side of the heart can appear as masses behind the anterior tricuspid leaflet.

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Problems with Prolonged Endotracheal Intubations

To the Editor:

We will attempt to answer Cash's question concerning long-term endotracheal intubations. His question asked what damage is done to the vocal cords (during long-term intubations of up to ten days).

We have recently looked at this problem in a large number of patients in intensive care units and have compared the degree of laryngeal pathologic abnormalities in both oral and nasal endotracheal intubations. Damage to the vocal cords occurs routinely following both oral and nasal intubations. As alterations in the microscopic surface are found to occur after two hours of intubation and macroscopic changes after six hours, it is apparent that laryngeal damage increases in severity as the duration of intubation increases. The injuries to the vocal cords that we observed during the five-day to nine-day intubations (Fig 1 and 2) included posterior ulcerations and cratering of the vocal cords, maceration of the vocal cords, ulceration of the arytenoid cartilage and corniculate tubercle, ulceration of the glottic surface of the epiglottis, ulceration of the proximal posterior tracheal wall approximating the glottic opening, supraglottic edema, abnormalities of glottic closing, anterior adhesions of the vocal cords, and laryngeal webs.

During our study, we carefully followed the development of laryngeal injury using the fiberoptic bronchoscope. Every 48 to 72 hours during intubation and within 24 hours after extubation, the vocal cords and surrounding laryngeal tissue were directly visualized. If we believed that the severity of laryngeal injury would cause prolonged phonation or functional impairment (or both), we recommended that tracheostomy be performed by our surgical colleagues. In long-term follow-up examinations, we have found that the majority of the laryngeal injuries will heal within a period of two weeks to approximately two months. Our major concern has been with the loss of functional integrity of the laryngeal apparatus, which may result in acute problems of aspiration within 48 hours following extubation or in a chronic process of aspiration.

We found that the route of intubation, as well as the duration, appeared to be a significant factor in establishing the severity of laryngeal injury. Nasal endotracheal tubes produced approximately 50 percent less laryngeal injury than oral endotracheal tubes. We believe that nasal tubes produce more stability and are less affected by the patient's movement of his head. Nasal endotracheal tubes are usually 0.5 to 1 mm smaller in diameter than oral endotracheal tubes and, therefore, produce less laryngeal injury because of their size. The majority of patients intubated in our study exhibited ulceration and cratering, which is due to the posterior force that the endotracheal tube exerts on the posterior laryngeal apparatus. This pressure is caused by the lever action of the tube as it bends over the tongue in an oral intubation and over the palate in a nasal intubation.

We had hypothesized that anatomic variants involving the length of the hard palate, the position of the first cervical vertebrae, and other factors might be important in explaining the variability of damage seen in patients; however, despite careful cephalometric analysis of 17 patients, we could detect no certain aggravating factors.

Although laryngeal damage was found after all prolonged intubations, our study demonstrated long-term oral endotracheal intubations produced significantly greater laryngeal injury than nasal intubations. There-

![Figure 1. Injury to vocal cords.](image1)

![Figure 2. Injured larynx, showing evidence of ulceration, cratering, and maceration of vocal cords and cartilaginous edema.](image2)
fore, we recommend nasal intubation in all adult patients requiring long-term pulmonary support via an endotracheal tube. Furthermore, we suggest that a decision to perform tracheostomy should be based upon concrete factors following inspection of the laryngeal apparatus with the fiberoptic bronchoscope, rather than upon some arbitrary duration of intubation.

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Chronobiologic Studies on the Cardiovascular System*

To the Editor:

We read with interest the editorial entitled “Sleep and the Cardiovascular System,” where Ferrer emphasized that “nocturnal problems in cardiovascular diseases have bases in normal fluctuations.”1(196) Actually, several studies have been performed concerning circadian rhythms in the cardiovascular system. A review of these works has been published by Smolensky et al.2 In addition to these, we have also published research in this field. Two years ago, we attacked the problems of the chronophysiologic and chronopharmacologic of the cardiovascular system.

In the field of chronophysiologic, we performed some experiments using five healthy young men synchronized with a nocturnal rest from 11 PM to 7 AM which demonstrated (according to Wertheimer2) a circadian rhythm statistically significant by the Cosinor test3 for some measurements of ventricular function, such as left ventricular ejection time and the Weissler index (left ventricular ejection time index), with acrophases (ie, the peak timing of the variable) between 2:30 and 4 AM. Considering that left ventricular ejection time represents an indirect measure of cardiac contractility, it can be stated that under standard conditions a decrease of cardiac contractility occurs at the same time of day.4

These data can have value only with a view to extending the study to ascertain if a similar rhythm is present in


480 COMMUNICATIONS TO THE EDITOR

CARDIOvascular patients or not and to determine how the data eventually can be modified by administration of drugs. Accordingly, we have studied the possible presence of a circadian rhythm in the pharmacokinetics of β-methyldigoxin after oral administration of a single dose in six healthy men. β-Methyldigoxin (1 mg in elixir) was administered every week on the same day, but at six different hours each time. Levels of digitalis in the serum were measured by radioimmunoassay of samples of blood taken at 0, 0.5, 1, 2, 4, 8, 12, 20, and 36 hours from ingestion. The limits of variability of the 36 total areas under the concentration-time curve obtained were 109.87 to 34.6 ng/ml/hr. The Cosinor test for total areas (indexes of bioavailability) reveals a statistically significant circadian rhythm with the acrophase at 10:05 AM. This means that a single dose of β-methyldigoxin given at different hours of the day can be absorbed differently in the same subject.

The examination of the individual curves for serum reveals that the curves obtained with a nocturnal administration of β-methyldigoxin have an exponential phase, whereas those obtained with diurnal administration do not present this exponential phase but instead have a late second peak 12 to 20 hours after the time of ingestion. A circadian rhythm of the area of the second peak by the Cosinor test is seen with the acrophase at 10:07 AM, similar to the acrophase of the total area. Also, the values for total area and the second peak area are significantly correlated (r = 0.95; P < 0.001). A few other authors previously described a second peak in levels of cardiac glycosides in the serum,5,6 suspecting a metabolic conversion to digoxin or metabolites (or both) by the liver or gastrointestinal flora (or both). This hypothesis was not confirmed by our results obtained via administration of digoxin; in fact, the latter has a second peak very similar to β-methyldigoxin. Moreover, the late second peak in our studies always occurred around 4 to 8 AM, independent of the hours of administration. This suggests the activation of an unknown third compartment strictly related to the light-dark rhythm. These results are opening new stimulating areas for investigation, which are already the object of our studies (data presented at Satellite Symposium on Chronopharmacology, Seventh International Congress of Pharmacology, Paris, July 22, 1978).

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