Minuscule Review

Chronobiologic Aspects of Transplantation


Human heart rate exhibits a circadian rhythm—a fact presumably known to Galen (Pieron H: Le problème physiologique du sommeil, Paris, Masson et Cie, 1913; Menzel W: Menschliche Tag-Nacht-Rhythmik und Schichtarbeit. Basel, Benno Schwabe and Co., 1962, p 23). This rhythm persists under diverse conditions—weightlessness in extraterrestrial space (Space Life Sciences 2: 18, 1970), rest in bed (op. cit.), and isolation in caves (J Physiol [Paris] 59: 117, 1967). It is found even in a child comatose for several months and amenable in this condition to synchronization by physical therapy (Physiologist 10: 230, 1967). It is the more interesting, therefore, that a morning minimum and evening maximum also characterized a human heart homograft monitored for 72 hours by Kraft and associates. This important report suggests that a totally denervated human organ not only has a circadian rhythm but also can be humorally synchronized with the social routine. That circadian cardiac rhythmicity as such is endogenous is suggested by its reported occurrence in the isolated mammalian heart (Tharp G, Folk GE: Comp. Biochem Physiol 14: 255, 1965) and even in the in vitro response of this heart to acetylcholine (Spoor RR, Jackson BB: Science 154: 782, 1966).

A critical question for the practice of transplantation is first whether an impending rejection may be signaled by alteration in rhythm. Such dyschronism may consist of altered time relations between the recipient and donor cardiac tissues which in the normally functioning heart ought to be synchronized in frequency and perhaps in phase. In the case reported by Kraft and associates was the synchronization with a presumably small difference in phase of about 2 hours (reported as 135 min) maintained until death? If not, would the maintenance of certain desirable phase relations among various rhythms lower the chances of eventual rejection? Another practical question is whether there is an optimal circadian time (at the outset) when some of the later difficulties still associated with transplantation may be overcome, that is, when rejection rates may be lower.

In any event, on the basic side, many additional questions remain to be investigated. Is the rejection of hearts from donors on the same routine as the recipients, lower than that of hearts from donors who are not? For example, what happens if the donor, as compared to the recipient, is phase-shifted in terms of routine to a varying extent, up to 180 degrees?

Studies on experimental animals and more clinical work on the possible merits of timing transplantation of various organs according to rhythms are overdue, even if, in terms of priority among chronobiologic endeavors, transplantation itself must take second place to preventive auto-rhythmometry, instituted before a vessel is obstructed or before an organ as a whole fails. (Abstracts of 2nd Interdisciplinary Cycle Research Institute Conference, Noordwijk, Netherlands, June, 1970).

FRANZ HALBERG, M.D.
Lusus Naturae

The right subclavian artery arising as the fourth branch of the aorta as a cause of dysphagia is rare, and the report of its interposition between the trachea and esophagus is most unusual. Bayford's historic case is well described but still is not entirely readily understood.

Jane Forham was born ... in the last year of the last century. From her infancy she was observed to have some difficulty in swallowing; but it was not much attended to till she entered into her thirteenth year ... At this time it became so considerable, as induced her to have recourse to medicine for relief; but she received no sensible benefit from any thing except repeated bleeding. ... She went on in this way, with the disease gradually increasing, for many years; during which time she constantly observed that her difficulty of swallowing was increased by violent exercise. ...

For the last twenty years of her life, this poor creature could scarcely from day to day muster up resolution to force down food to prevent her starving. ... Upon these occasions she always experienced violent palpitations of the heart. ... Different kinds of food made no sensible difference in the effects, except that solids gave her less uneasiness than fluids. ... Being worn out with fatigue and famine ... she sunk into her grave in the beginning of February 1761 [age 62].

... The cavities of the thorax and abdomen were fully examined; but to my great disappointment, neither in them nor in the oesophagus, or parts adjacent, was there the smallest appearance of disease. ... At length, by mere accident I discovered an extraordinary lusus naturae in the disposition of the right subclavian artery. ...

If ... the unusual situation of the right subclavian artery be considered as the sole cause of the obstruction in deglutition, a new species of dysphagia is hereby established; which may be called lusoria, from the Lusus Naturae that gives rise to it.—

Minuscule Review

The 13th supplement of Acta Cardiologica: Symposium on Coronary Collateral Circulation and on the Assessment of Antianginal Drugs, arrived in my office this month. Although it is 3 years since the symposium was held, the now available proceedings provide basic reference data in this active field of investigation. Possibly the research work from European laboratories will not have been well known to many American investigators and the supplement may become for them, in particular, an informative volume. The table of contents is given below.

H. B. B.

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ROUND TABLE DISCUSSION
Minuscule Review


In investigations characterized by superb design and masterful attention to detail, the authors have demonstrated pulsatile uptake of CO in the human lung, indicating that the pulmonary capillary volume has a systolic tide. The work follows by 5 years that of the senior author with Lee, in which the pulmonary flow was found to be pulsatile; an observation concordant with the finding of a near equivalence of pressures across the normal human pulmonary vascular bed at the end of diastole. The present report improves one’s visualization of the dynamics of the circulation in the normal lung. One wonders whether the complicated technic could be applied to patients with an abnormal pulmonary circulation, e.g., pulmonary hypertension of various types. The intriguing question arises concerning individuals with gross mitral regurgitation and a low pulmonary vascular resistance, as to whether there might be a temporal dissociation of the peaks of pulmonary blood flow and of capillary volume, or possibly of two peaks of increased CO uptake being present in the plethysmographic records. It is expected that the publication of Dr. Menkes and associates will become a standard reference for pulmonary physiologists and physicians interested in pulmonary hemodynamics.

H.B.B.
Chronic Obstructive Lung Disease in Fiction

(The “Blue Bloater”)

The Major, who had been blowing and panting all the way down, like another engine, and whose eye had often wandered from his newspaper to leer at the prospect, as if there were a procession of discomfited Miss Toxes pouring out in the smoke of the train, and flying away over the fields to hide themselves in any place of refuge, aroused his friend by informing him that the post-horses were harnessed and the carriage ready.

The Major, more blue-faced and staring—more over-ripe, as it were, and giving vent, every now and then, to one of the horse’s coughs, not so much of necessity as in a spontaneous explosion of importance, walked arm-in-arm with Mr. Dombey up the sunny side of the way, with his cheeks swelling over his tight stock, his legs majestically wide apart, and his great head wagging from side to side, as if he were remonstrating within himself for being such a captivating object.—From Dickens C: Dealings with the Firm of Dombey and Son: Wholesale, Retail, and for Exportation. London, Chapman & Hall, Ld. (First published in 1848), 1901, pp 242, 243.
Early Report of Atrial Flutter
Recorded Waves from Cervical Veins and Cardiac Apex

Case I. The jugulo-carotid and apical tracings present a series of rhythmic, positive waves, the rate of which is about 255 per minute. The ventricles contract rhythmically 32.2 times per minute.—From: JOLLY WA, RITCHIE WT: Auricular flutter and fibrillation. Heart 2: 177, 1911.
Minuscule Review


In both of these papers the clinical use of the radioimmunoassay of plasma digoxin was described. The assay was found to be simple, rapid (3 hours or less), and accurate.

In the first paper only a rough correlation was demonstrated between the total daily dose of digoxin and the plasma level, and the therapeutic range of plasma levels in nontoxic patients was found to be wide (<1 to >5 ng/ml).

In the second paper digoxin levels were studied in 116 patients with atrial fibrillation but without digitalis toxicity, and in 22 additional patients with digitalis toxicity. The mean digoxin plasma level was 1.4 ng/ml in the nontoxic group and 3.1 ng/ml in the toxic group. Overlapping of plasma levels in the two groups was great in the range of values between 2 and 3 ng/ml, although below and above this range the groups had virtually completely separated values. A definite, but statistically weak inverse relationship was found between ventricular response rate and plasma digoxin levels in the fibrillation group.

The young and the elderly patients had comparable therapeutic digoxin levels, but the elderly patients required lower maintenance doses to maintain these levels. This observation was attributed to a postulated decrease in renal digoxin losses in the elderly. It was also shown that a number of the clinically nontoxic fibrillation patients had high digoxin levels suggesting that they had a high potential for developing overt toxicity.

Both papers point up the clinical assets and liabilities of digoxin assays. The assays are eminently practical. Interpretation of the results for the individual patient data, however, is difficult because the relationships between plasma free and bound glycoside and cardiac "receptor" binding and between "receptor" binding and toxicity are unclear and most probably show considerable variability from patient to patient.

ARTHUR H. L. FROM, M.D.
Historic Annotation

Reappraisal of Digitalis Therapy in Dropsy by an Early London Doubter and Critic of Withering

Since the first edition of these Memoirs [1789] appeared, a sufficient period has elapsed to afford a more accurate knowledge of the medicinal effects of the digitalis purpurea. The cautions contained in the preceding account have been of use, in guarding against temerity, on one hand, and encouraging, on the other, prudent experiment. That this medicine is a powerful diuretic, was suggested, and future enquiry has confirmed, as well as its dangerous sedative powers; but under the direction of medical skill, I consider it as one of the most powerful diuretics in medicine, and efficacious remedies in ascites and dropsical affections, as far as diuretics can act as curative remedies. . .

I cannot dismiss this subject, without mentioning that I have found the digitalis a very important remedy in the hydrops pectoris. . .—From: Lettsom JC: Of the digitalis purpurea, in hydropic diseases. Memoirs of the Medical Society of London, ed 2, 1794, vol 2, p 177.

Circulation, Volume XLII, November 1970
Minuscule Review

Schneller GH: Status report on drug bio-availability.

The question as to whether a drug marketed under proprietary name, as compared to one with a generic name, can be assumed to be equivalent in therapeutic efficiency remains a live issue amongst medical and pharmaceutical professions. Dr. Schneller reviews recent developments in biopharmaceutics in respect to the effectiveness of drug products. The term "bio-availability" may be a new one to the medical profession. The author includes a table listing 40 drug substances which have been shown to have, or suspected of having, variable efficacy dependent upon their biologic availability. For those interested in reviewing the problem the list of references will be of great value.

H.B.B.
The Montpellier group presents its findings on atrial depolarization, by means of direct and semidirect exploration of the atria during more than 15 years of studies, in 45 cases of classical atrial flutter and in nine of atrial tachycardia. The modes of activation are shown to be quite different, thus supporting separate nosologic categories for the two arrhythmias.

Simultaneously recorded leads II, III, V_F, V_1, V_3, and V_6 provided morphologic criteria for the distinction and served as chronologic references for exploring electrodes. Of the latter, 2 to 4 simultaneously recording ones in the esophagus and coronary vein explored the left atrium; another 2 to 5 were inserted into the right atrium. Data from such sources permitted analysis of the various sites, direction, and duration of atrial activation. In every case atrial rhythm was perfectly regular, atrial rates were 200 to 330/min, and A-V block was 2:1 or greater.

In atrial flutter of the common type, limb leads showed diphasic waves with prominent negativity in II, III, and V_F; the negative portion of the atrial wave in V_6 preceded the positive wave in V_1. In such classical instances, the wave of activation ascended the left atrium and interatrial septum briskly, then descended the right atrial lateral wall more slowly; the entire atrial cycle was occupied in activation at appropriately successive sites. In three patients, including two with grossly dilated right atria, the atrial rates were only 200 and 230/min, but the findings nevertheless were as just described, including re-excitation with a counterclockwise progression (frontal and left sagittal planes). In a single case of atypical flutter, the atrial wave was positive in V_6 and followed that of V_1; limb leads were like those in classical flutter, but activation proceeded in a clockwise fashion. Successful cardioversion in common flutter revealed that excitation of the lateral wall of the right atrium in flutter was similar to that in sinus rhythm, but of reduced velocity. Slower atrial rates were related to prolongation of excitation in the right atria, not the left.

In the nine cases of atrial tachycardia (alias nonflutter, rare flutter, or atrial tachysystole) atrograms were positive in the frontal plane and in V_6, and variable but usually positive in V_1; the atrial rates were in the usual flutter range, 250 to 300/min. Activation was entirely different from that of flutter, in direction and duration of depolarization. Activation proceeded from the cephalic portion of the right atrium distally over both atria synchronously, with a total duration never exceeding 0.12 sec, of the 0.20 to 0.24-sec cycles. In the same patients after cardioversion depolarization was similar, allowing speculation that the site of ectopic focus had been near the S-A node.

Other observations include those on atrial fibrillation, flutter-fibrillation (basically fibrillation, but with relatively organized and almost rhythmic excitation in a portion of the right atrium), and the effects of rapid electrical stimulation on the flutter wave (temporarily increased rate, sometimes conversion to fibrillation).

In brief, this report of elegant studies in man shows that excitation in classical flutter persists throughout the entire atrial cycle and proceeds upward in the left atrium and downward in the anterolateral right atrium in a continuum compatible with that of an entrapped circuit wave; in contrast, the mechanism of atrial tachycardia is that of an ectopic focus. Differentiation is never possible on the basis of atrial rates alone, and may depend upon analysis of multichannel tracings including those obtained by direct or semidirect atrial exploration.

David A. Rytand, M.D.
best way to the solution of the coronary heart disease problem.

Acknowledgment

Dr. Knut B. Westlund, Life Insurance Companies' Institute for Medical Statistics at the Oslo City Hospitals, provided mortality data and helped with statistical analyses. Mrs. Vera Haakenstad and Mr. Käre Porsböll gave skillful technical assistance in the preparation of the manuscript. To all these and many others I express my warm gratitude.

References


Early Judean Clinical Trial in Diet

Then Daniel said . . . "Test your servants for ten days; let us be given seeds to eat and water to drink. Then let our appearance and the appearance of the youths who eat the king's rich food be observed by you, and according to what you see deal with your servants." So he harkened to them in this matter, and tested them for ten days. At the end of ten days it was seen that they were better in appearance and fuller in the flesh than all the youths who ate the king's rich food. So the steward took away their rich food and wine they were to drink, and gave them seeds. (Daniel I: 10-16)—From Israel J Med Sci 1: 399, 1965.
Minuscule Review

Abernethy J: Account of two instances of uncommon formation in the viscera of the human body.

Continuity of the inferior vena cava with the azygos vein has a strong association with polysplenia and a tendency for faulty arrangement of body organs.

In studying the literature, we sometimes find that the "old timers have stolen our best ideas." Thus Abernethy, almost 200 years ago in the Transactions of the Philosophical Society of London, described and illustrated continuity of the inferior vena cava with the azygos vein and symmetry of the liver (fig.) in an infant, assumed to be about 10 months old. While no intracardiac anomalies were found, faulty orientation of the heart was present.

"The situation of the heart was reversed; the basis of that organ was placed a little to the left of the sternum, whilst its apex extended considerably to the right, and pointed against the space between the sixth and seventh ribs. The cavities usually called the right auricle and ventricle were consequently inclined to the left side of the body; therefore, to avoid confusion in the description, I shall... term them anterior, whilst those cavities usually called left, I shall term posterior. The inferior vena cava past [sic.], through a tendinous ring in the right side of the centre of the diaphragm, it afterwards pursued the course of the vena azygos, the place of which it supplied; after having united with the superior cava, the conjoined veins passed beneath the basis of the heart, to expand into the anterior auricle. The veins returning the blood from the liver united into one trunk, which passed through a tendinous aperture in the left of the centre of the diaphragm, and terminated immediately also in the anterior auricle." As part of faulty situs, the aortic arch was right-sided, with mirror image branching.

Abernethy's description of the spleen takes on special significance at present: "The spleen consisted of seven separate portions, to each of which a branch of the splenic artery was distributed. The other viscera were sound, and of their usual structure and appearance."

Deserving emphasis also is the description of the portal and umbilical veins: "The vena portarum was formed in the usual manner, but terminated in the inferior cava, nearly on a line with the renal veins. The umbilical vein of this subject ended in the hepatic vein."

The last quotation may be used to suggest to pathologists of the 20th and 21st centuries that they exercise particular care in identifying the visceral veins of the abdomen when dealing with the "splenic syndromes."

JESSE E. EDWARDS, M.D.

(Left) Symmetry of liver (N). The portal vein (T) joins the inferior vena cava. Inversion of all cardiac chambers with anatomic right ventricle (A) and right atrium (B) lying on left side. E = superior vena cava; F = ascending aorta. (Right) Inferior vena cava (B) continuous with azygos vein joins the superior vena cava (D) which lies on the right, F, described by Abernethy as conjoined veins passing beneath the basis of the heart to the anterior (anatomic right) auricle is strongly suggestive of a coronary sinus carrying blood from the right-sided superior vena cava to the left-sided anatomic right atrium. K = hepatic vein joining anatomic right atrium; T = portal vein joining inferior vena cava.
William Withering
By Carl Fredrick von Breda
Breda pinxit 1792
(Courtesy Nationalmuseum, Stockholm)