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Contractile state and myocardial oxygen consumption of the isolated feline left ventricle

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In isolated cat hearts, perfused with blood from donor cats, a balloon was introduced via the atrium into the left ventricle. Balloon volume could be changed during contraction with a membrane pump. Left ventricular oxygen consumption ($M\dot{V}_{O_2}$ in $\text{cm}^3 \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$) was measured during isovolumic and zero load contractions, at different end-diastolic balloon volumes (V_{ed} in cm^3). Heart rate was kept at 2.5 Hz. In 6 experiments we studied the effect of two different calcium concentrations of the arterial blood. We found for zero load contractions that $M\dot{V}_{O_2} = 3.19 \pm 0.20 V_{ed}$ at a $[\text{Ca}^{+}]_o$ of 0.91 mM and that $M\dot{V}_{O_2} = 4.71 \pm 0.37 V_{ed}$ at a $[\text{Ca}^{+}]_o$ of 1.81 mM. Isovolumic contractions, generating pressure gave $M\dot{V}_{O_2} = 2.84 \pm 1.17 V_{ed}$ and $M\dot{V}_{O_2} = 4.51 \pm 1.14 V_{ed}$, respectively. These findings imply, that for zero load contractions, $M\dot{V}_{O_2}$ changes little with V_{ed} at low $[\text{Ca}^{+}]_o$. This dependency is somewhat stronger at higher $[\text{Ca}^{+}]_o$ but not significantly different ($p > 0.05$; paired t-test). Isovolumic $M\dot{V}_{O_2}$ depends much more on V_{ed} , but this dependency remains also unchanged when $[\text{Ca}^{+}]_o$ is increased ($p > 0.05$; paired t-test). In 6 experiments $[\text{Ca}^{+}]_o$ was varied over a wide range during zero load contractions at $V_{ed} = 0$. For $[\text{Ca}^{+}]_o$ higher than 5.0 mM no further increase in oxygen consumption was found. We conclude that contractile state, varied by $[\text{Ca}^{+}]_o$, is an independent determinant of myocardial oxygen consumption.

Structure and function of the sinoatrial node

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The impulse in the sinoatrial node is generated by cells that contain relatively few myofilaments in the rabbit, the guinea-pig and the cat. These so-called primary pacemaker cells give therefore a rather 'empty' impression. The area of relatively low-myofilament density is substantially larger than the primary pacemaker area. The area of earliest discharging cells with identical action potential configuration is considered as the primary pacemaker area. From the primary pacemaker towards the periphery there is a more abrupt transition in electrophysiological parameters than in morphological parameters. There is a large difference in the ratio of collagen to myocytes between the cat on one hand and the guinea-pig and the rabbit on the other hand. In the cat more than 50% of the nodal volume is occupied by collagen. In the rabbit and the guinea-pig more than 50% is occupied by myocytes.

Electrophysiological disturbances underlying atrial fibrillation

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The activation sequence during acetylcholine induced atrial fibrillation (AF) was studied in isolated Langendorff perfused canine hearts by recording simultaneously from 192 endocardial leads. Series of activation maps were constructed covering 1 sec of persistent AF. These maps clearly demonstrated that AF was based on the presence of multiple circulating wavelets. However, the number of waves at any particular moment during AF varied considerably. New wavefronts were continuously formed by division at areas of temporary conduction block, while other wavelets ceased to exist either due to fusion with other waves or because of extinction at the A-V ring. To characterize this balance between waxing and waning of wavelets during persistent AF, we actually counted the number of

wavelets at intervals of 10 msec. In both atria 6 wavelets were present, varying between 3 and 10. There was no difference between the right and the left atrium. Each atrium accommodated 3 wavelets, ranging between a maximum of 5 and a minimum of 0. The temporary arrest of fibrillation in one atrium did not cause termination of AF, because it was immediately reinitiated from the other atrium. On the other hand it shows that the presence of 3 multiple wavelets is *not* sufficient for the persistence of AF.

Physiological changes during whole body hyperthermia for the treatment of malignancies

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Since Von Ardenne published his therapy scheme (multistep therapy program) for the treatment of cancer in the early fifties interest for combination of radiotherapy with hyperthermia has been very large. During recent years knowledge of anesthesia and insight into the physiological effects of hyperthermia has reached such a level that vital parameters can be much better interpreted, measured and registered and necessary correction immediately performed adequately. Since 3 years whole body hyperthermia is performed in Rotterdam as a preparation for effective radiotherapy in extensive malignancies. Intensive cardiovascular studies were done in 30 patients during hyperthermia treatment. The patients were anesthetized with nitrous oxide/oxygen, relaxation and then were warmed up for 2 h in a modified Siemens hyperthermiacabin to a temperature of 41.8°C. Hyperthermia induced a great increase in cardiac output and heartwork with decrease of peripheral resistance in the systemic as well as the vascular bed of the lungs. The arterial pulmonalis pressure increased while the systemic blood pressure decreased. The result was a proportionally greater increase in right ventricular work as compared to a much less increased left ventricular work. Oxygen consumption went up with 34% from which a major part was due to the increase of heartwork. Furthermore significant changes of hematocrit, electrolytes and serum enzymes were seen. Based on the data gained in patients and animal experiments it can be concluded that the liver is the limiting organ for treatment with whole body hyperthermia.

Individual variation in the serum cholesterol response to dietary cholesterol in man and laboratory animals

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Differences in the response of serum cholesterol to dietary cholesterol in rabbits and rats have a genetic basis. In inbred rabbits a 5-fold greater response was found in two hyper-responsive strains than in two hyporesponsive strains. Similar differences in serum cholesterol response between inbred strains of rats were also observed. In order to see whether humans exist with a consistently high or low serum cholesterol response to an increase in cholesterol intake, we have carried out three controlled dietary trials with the same subjects. Although the response in each individual was only partly reproducible from one study to another, the hyperresponders consistently showed a significantly higher serum cholesterol response in the second and third trial than the selected hyporesponders. We conclude that human hyper- and hyporesponders do exist. We have investigated whether differences in responsiveness are related to differences in endogenous cholesterol synthesis. In rats on a low cholesterol diet whole body cholesterol synthesis (measured as faecal excretion of bile acids and neu-

tral steroids plus cholesterol retention minus intake) was about 2-fold higher in a hypo- than in a hyperresponsive strain. In humans, cholesterol synthesis on a low-cholesterol diet, measured as faecal excretion minus intake, was also negatively associated with the response of serum cholesterol to dietary cholesterol. These data suggest that hyperresponders have a limited range for down regulation of cholesterol synthesis after cholesterol loading, and this may partly explain the high cholesterolemic response in such individuals. Supported by grant No. 31.013 of the Netherlands Heart Foundation and an established investigatorship to M.B.K.

Individual differences in the circadian system response to shifts of the social zeitgeber

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Morning-type (M-type) and evening-type (E-type) persons not only differ in the external phase position of circadian rhythms, but also in the internal temporal order of these rhythms. (G. A. Kerkhof, Inter-individual differences in the human circadian system. A review. Biological Psychology (1984) in press). The role which these individual differences play in the response of the circadian system to external disturbances forms the main object of the present study. During a 12-day period – from 6 days before until 6 days following the 1-h changes from East-European Time to Mid-European Time (autumn 1982) and vice versa (spring 1983) – samples of M-type and E-type subjects kept daily records of their hours of sleep, and – as frequent as possible – hourly self-measurements of oral temperature and subjective alertness. The major effects of these clock time changes occurred in response to the advance change (i.e. in the spring). For M-types, the alertness rhythm followed with a delay of 2 days, while the other two rhythms changed their phase instantaneously; for E-types, however, the temperature rhythm was delayed for 3 days.

On-line registration of physiological data during closed circuit anaesthesia

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Anaesthesia with a closed circuit system is discussed since 1924, but has never been so far developed that it could be performed with automatically controlled ventilation. On the basis of the rolling seal rebreathing respirometer we have developed at the Erasmus University Rotterdam the first fully automatically controlled closed circuit system. Volume loss is registered by the piston which does not reach its endposition at the end of expiration and supplemented by an electronically feedback controlled injection of N_2O , thus the total volume is kept constant. At the same time the inspiratory oxygen concentration is kept constant on a preset value, feedback controlled. The closed circuit system is fully separated from the ventilator system so that any type of ventilator can be used to drive the respirometer externally. As volume and inspiratory oxygen concentration are kept constant the new system offers the possibility to add several parameters to patient monitoring:

1. Exact registration of gas uptake from breath to breath (e.g. \dot{V}_{O_2} , \dot{V}_{CO_2}).
 2. Registration of a constant fraction of inspiratory gases independent of minute volume and gas uptake.
 3. Registration of several important cardiorespiratory parameters based on noninvasive rebreathing techniques, e.g. functional residual capacity, ventilation distribution ratio, cardiac output.
- Further development of the possibilities of the automatically controlled closed circuit system will decisively enlarge the scale of measurable vital physiological parameters of seriously ill patients in the operation room and on the intensive care unit.

Results of an investigation on the origin of heart sounds with the aid of phono-echocardiography and multi-site phonocardiography

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Origin of heart sounds has been studied from two different points of view. Temporal relationship of heart sounds to valvular motion has been investigated by using combined phono- and echocardiographic techniques: typical discernible vibration patterns have been related with events in echocardiographic tracings, especially those connected with valvular opening and closure. On the other hand, spatial vibratory patterns have been investigated by applying multi-site recording of phonocardiographic signals at 49 chest wall points, homogeneously distributed at the precordial area. Wave form parameters such as norm (vibration intensity), correlation value (vibration similarity with respect to the signal measured at a chosen reference point) and reconstruction value (vibration similarity with respect to all observed chest wall points) have been calculated for well defined intervals of the heart cycle. These parameters connected with appropriately chosen intervals reveal typical spatial distributions. E.g., phase reversal of the aortic component of the second sound is perfectly indicated by correlation and reconstruction distribution, the latter showing a clear minimum at the chest wall site where the phase reversal occurs. Combining both methods, the first one giving reliable temporal information in connection with valvular motion, the second one supplying information about spatial vibratory distribution and thus allowing discrimination between effects of different physiological vibration sources, will contribute to the understanding of the physical mechanisms of heart sound generation.

The development of coupling between heart cells in tissue culture

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Neonatal rat heart cells, when isolated in tissue culture, beat spontaneously and irregularly. When two such cells grow together they synchronize their rate of beating. We analyzed the emergence of this synchronization of beat rate. Before physical contact between a pair of heart cells is existent each of them beats in its own irregular rate; the degree of irregularity is a function of the mean inter beat interval (IBI): the smaller the IBI, the smaller the degree of irregularity. Once physical contact is made by the growing cells synchronization occurs most often from one beat to another. In some cases a short period of partial synchronization is observed during with 1:2, 1:3, etc. modes of synchronization are present. In virtually all cases studied the common mean IBI of the pair is intermediate between the mean IBI of each of the originally single isolated cells. There is a strong correlation between the mean IBI of the pair and that of the originally fastest beating cell. Sometimes the cellpairs beat at the same rate but not synchronous: the originally faster beating cell leads the originally slower one by some tens of milliseconds. We presume that in these cases the amount of coupling between the two cells is less than between really synchronously beating cells. Contrary to literature reports stating otherwise, these observations tend to support the classical pacemaker hypothesis.

Temporal adaptation of reflex changes in heart rate during chronic infusion of vasoactive drugs

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The chronotropic effect of calcium entry blockers on the heart depends on the interaction between the direct negative chronotropic effect and the indirect reflex tachycardia due to hypotension. Resetting of the baroreceptor reflex may change the