The normal range and determinants of the intrinsic heart rate in man

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Abstract

Jose and Collison published a study on the normal range and the determinants of intrinsic heart rate in man in Cardiovascular Research in 1970 [Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res 1970; 4: 160–167]. The intrinsic heart rate is the heart rate under complete pharmacological blockade. They showed that (i) the resting heart rate is lower than the intrinsic heart rate and that (ii) the intrinsic heart rate declines with age. They also established that the variability in intrinsic heart rate between individuals of the same age is of the same order as the effect of ageing at the population level. This update discusses the relevance of these data with emphasis on sinus node function and autonomic balance. The paper of Jose and Collison was cited more than 200 times. The frequency of citation started to increase more than 10 years after publication. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

In 1970 Jose and Collison published a study on the normal range and the determinants of the intrinsic heart rate in man in Cardiovascular Research. [1]. They did not only study ‘intrinsic heart rate’, which they defined as the heart rate under the simultaneous presence of the non-selective β-adrenoceptor antagonist propranolol (0.2 mg/kg) and the muscarinic receptor blocker atropine (0.04 mg/kg), they also established the inverse relation between age and intrinsic heart rate. Furthermore they made separate analyses in females and males. Therefore the paper included – apart from the measurement of the intrinsic heart rate itself – additional important pieces of information for later studies on areas varying from sinus node dysfunction, autonomic balance, heart rate variability, gender and aging (see preceding historical note [2]). The authors could have made their paper even more attractive by choosing another title. Fig. 1 taken from the original paper [1] shows the relation between age and intrinsic heart rate in normal males and females. Both in males and females the intrinsic heart rate decreases, on the average, from 107 beats/min at 20 years to 90 beats/min at 50 years. At the same time Fig. 1 shows that the intrinsic heart rate has 95% confidence limits of ±15%. This implies that the variability between individuals of the same age is of the same order as the decrease of the mean intrinsic heart rate of the whole population over about 55 years. In other words, the intrinsic heart rate of an individual of 20 years may actually be lower than that of another individual of 50 years. Obviously, this sets limits to the significance of the aging induced decrease in heart rate.

The interest of the authors in the pharmacological concept of intrinsic heart rate had been raised by previous work of Jose published in 1966 [3] and of Jose and Taylor published in 1969 [4]. In those studies it had already been established that heart rate becomes fixed under the combined presence of atropine and propranolol, which is considered to cause complete autonomic blockade. However, propranolol only partially interferes with the activity of the sympathetic limb of the autonomic nervous system, because it blocks β-adrenoceptors but not α-adrenoceptors. Furthermore, there is a classic, small, but convincing literature which claims that vagal chronotropic effects include – apart from the well known negative components mediated by acetylcholine – also positive, i.e. acceleratory, components (see section on autonomic balance). The previous studies [3,4] were directed to normal individuals as well as to patients with heart failure. Thus, Jose and Taylor [4] showed that the intrinsic heart rate is different
in normal individuals and in NYHA class I, class II and class III/IV patients. In normal patients (mean age 25 years) the intrinsic heart rate was 107 beats/min (comparable to the data in Fig. 1 taken from the paper published by *Cardiovascular Research* in 1970 [1]). In class III/IV patients the intrinsic heart rate was 79 beats/min in a subgroup of patients with nonvalvular heart disease and 75 beats/min in a subgroup of patients with aortic stenosis. The mean age of those patients was 50 years. The significance of the paper of Jose and Collison [1] is that the difference in intrinsic heart rate between normal individuals and patients with heart failure can partially be explained by the difference in age. The lower intrinsic heart rate in patients with heart failure thus may in part result from the underlying pathology. A lower intrinsic heart rate has also been demonstrated in dogs with heart failure (127 beats/min) compared with normal dogs (175 beats/min) [5]. A lower intrinsic heart rate in patients with heart failure may point to impaired sinus node function. A prolongation of cycle length in the isolated right atrium of rabbits with heart failure has indeed been demonstrated [6]. Moreover, the effect of the combined administration of propranolol and atropine, i.e. the difference between heart rate at rest and intrinsic heart rate, is different in normal individuals and in heart failure both in patients [4] and in dogs [5].

The data of Jose and Collison [1] have been confirmed by Alboni and colleagues [7] and extended to younger age by Marcus and colleagues [8].

Intrinsic heart rate can be assessed by three ways: (i) in vivo by pharmacological tools, (ii) in vivo by surgical interventions, (iii) in vitro after isolation of the whole heart (Langendorff perfusion) or the right atrium. Finally, cardiac transplantation is of interest, because those patients...
have two sinus nodes, one innervated (in a rim of remaining tissue of the explanted heart) and one de-nervated (the implanted-donor-heart).

2. Intrinsic heart rate and sinus node

The human heart beats about 100,000 times a day resulting in 2 billion heartbeats during a lifetime. Normally each cardiac activation originates from the sinus node which was discovered by Martin Flack and Arthur Keith in 1906 in the mole’s heart [9–11]. The relevance of this new anatomic structure was appreciated with little debate, because electrophysiological techniques, needed to verify the pacemaker hypothesis, were available at about the same time as the anatomical discovery of the sinus node [12–14]. The myogenic-neurogenic controversy with respect to cardiac automaticity started to be definitely settled in 1921 by Eyster and Meek [15].

2.1. Differences in heart rate between species

Specific metabolic rate, that is metabolic rate relative to body size, decreases in larger mammals [16,17]. Therefore cardiac output relative to body size also decreases in larger animals. Thus, it is a little surprising that all mammals have the same relative heart mass: about 0.6% of body mass [18]. Stroke volume, one of the two components of cardiac output, increases also linearly with body weight [16,17]. The decrease in relative cardiac output is solely brought about by the other component of cardiac output: heart rate. Fig. 2 (upper panel) shows the relation between body weight and cycle length according to the formula [17,19]:

\[ \text{BCL} = 0.249 \cdot \text{BW}^{0.25} \]  
(1)

with basic cycle length (BCL) in seconds and body weight (BW) in kilograms. Cycle length is thus longer (or heart rate lower) in larger species. Fig. 2 (upper panel) further shows that longevity (life span) also relates to body weight according to the formula [20]:

\[ \text{Life span} = 11.8 \cdot \text{BW}^{0.20} \]  
(2)

as far as mammals in captivity without the effects of predation or critical food supply are concerned. Interestingly, by dividing formula (2) by formula (1) we obtain the formula for the total number of heartbeats:

\[ \text{Total heartbeats} = 1.5 \text{ billion} \cdot \text{BW}^{0.05} \]  
(3)

Fig. 2 (lower panel) shows that the total number of heartbeats during the whole life is more or less similar in smaller and larger mammalian species, i.e. between 1 and 2 billion. Readers applying this formula to themselves, may be surprised to be still alive. The formula is not pertinent to humans, because we live much longer than expected from body weight.

How is it possible that the heart of a small animal beats so much faster than the heart of a larger animal? For instance, at one side of the mammalian spectrum of pacemaking we find the bat. During flight its heart rate may increase to more than 1000 beats/min [21]. More recently, by the interest in transgenic mice, data have become available on heart rate in freely moving mice. It is about 500 beats/min in rest [22,23] and it can easily increase to 800 beats/min ([22]; but see also Rappaport in Ref. [24]). Heart rate in big animals as elephants is about 25 beats/min [25] and in whales it can be well below 20 beats/min [24]. Are the intrinsic properties of the pace-
maker fibres in these species so very different, or does a longer cycle length, also result from the coupling of increasing numbers of more or less similar cells? Coupling of sinus node cells is a prerequisite for regularity, because isolated pacemaker cells have a variable beat-to-beat interval [26,27]. Also the sinus node beats faster if detached from the right atrium [28] and subdivision of a whole rabbit sinus node (7×2×0.3 mm) into small specimens (0.8×0.8×0.3 mm) renders numerous pieces with a substantially higher rate than the whole sinus node [27]. Coupling of more and more automatic elements thus results in lower heart rate. The decrease in intrinsic heart rate with age (Fig. 1) may result from changes in density of specific membrane currents (beyond the scope of this paper, but see [29–32]), intercellular coupling by specific connexins forming gap junctions (beyond the scope of this paper, but see [33,34]) and/or fibrosis (see next section).

2.2. Differences in nodal dimensions between species

In the previous section we have shown that larger hearts have lower heart rates. Also, we have seen that coupling of more pacemaker cells yields regularity, but also a lower rate. Thus, the question arises whether larger hearts have larger sinus nodes.

There is surprisingly little information on sinus node dimensions. As with the atrioventricular node [35], there is a tendency towards larger sinus nodal dimensions in larger animals (for review [36]). Thus, in rodents the nodal length is in the mm range [36], whereas reports on the length of the human sinus node vary from 7 mm [37] to 20 mm [14]. In cow and horse the length is 30 mm [38,39]. It is not clear, whether a larger sinus node is a prerequisite for pacemaking in a larger heart per se, or that, alternatively, a larger sinus node is a prerequisite to obtain a slower heart rate, which is necessary to maintain adequate pump function in a larger heart. It is emphasised that the boundaries of the SAN cannot be determined accurately.

2.3. Differences in heart rate with aging: collagen and myocyte content or intrinsic electrophysiological changes?

Electrical coupling is important for the automaticity of the sinus node, but also for driving the whole heart. Too much electrical coupling may lead to quiescence of the sinus node caused by the hyperpolarizing atrium, whereas too little electrical coupling may lead to a ‘pace, but not drive’ condition [40]. There are no data on the effects of aging on intercellular coupling to explain a change in intrinsic heart rate as observed by Jose and Collison [1]. Fibrosis may, however, present another parameter that may substantially affect intercellular coupling.

A substantial amount of collagen is present in the sinus node [41]. In normal human hearts the amount of collagen increases until 20 years [41–46]. According to some authors this gradual increase stabilizes at 20 years [46] or at 40 years [43], whereas a more gradual increase until 80 years [45] and a relatively late increase (above 70 years) have also been described [44]. This confusion is presumably explained by the fact that at any age the differences between individuals are more striking than the effect of aging itself [42,46]. Unfortunately, it is unknown whether the amount of collagen is of any value at all in assessing pacemaker function. There are both clinical [47] and experimental examples [48] of extreme structural abnormalities with apparently normal function. An increase in collagen content is not synonymous with a decrease in myocyte content, because collagen fibres may also substitute for fibroblasts or amorphous matrix. A decrease in myocyte content with age has been determined in normal hearts [41,43,49,50], but such a decrease would in itself not necessarily lead to a decrease in heart rate. Despite the availability of a relatively large amount of studies on collagen content, we cannot be sure that an increased amount of collagen explains the constant decrease in intrinsic heart rate with age as shown by Jose and Collison in Fig. 1 [1]. Even the large interindividual variability in intrinsic heart rate at any age (±15%, see Fig. 1) may be associated, but not necessarily causally related with the large interindividual variability in collagen content of human sinus nodes of the same age (see Fig. 4 in Ref. [46]). An experimental study in cat and rabbit sinus node has demonstrated that the rate of diastolic depolarisation decreases with aging [51]. Therefore decreased diastolic depolarisation of the sinus node with aging constitutes the only parameter with a causal relation with the decrease in intrinsic heart rate.

2.4. Differences between individuals within the same species of the same age

So far we have dealt with interspecies differences in heart rate and with differences caused by age. There are, however, also striking differences between individuals of the same species and age. In a selection of studies on isolated rabbit right atrium preparations sinus rate varied from 77 to 218 beats/min (Fig. 3 in Ref. [52]). A subselection of studies with identical temperature and extracellular K⁺ concentration still showed sinus rates from 114 to 185 beats/min [52]. These were averaged sinus rates in different studies in the rabbit. Fig. 3 (from Ref. [53]) shows that sinus rate of individual isolated rabbit right atria varies from 120 to 200 beats/min (cycle length 300–500 ms) within the same study. Lower and higher sinus rates probably result from different sets of membrane currents. Fig. 3 shows that this interindividual variability disappears when both the Na⁺ and Ca²⁺ concentrations are lowered by 50% resulting in a constant sinus rate of 143 beats/min (cycle length 418 ms). Apparently the intrinsic differences between individual
Adrenergic and non-adrenergic varicosities are found in Collison [1].

Nodal cells are 20±100 μm. Gaps between varicosities and vagal predominance results in a much lower resting heart rate in the instrumented conscious dog in general contain 5±15 axons. When the nerves become smaller and smaller they gradually lose the Schwann sheet and they end as naked axons in clefts near the sinus node [68,70,71]. There is a large interindividual variability disappears and cycle length is about 420 ms in sinus nodes from all animals (n = 10). Reproduced with permission of the American Society for Pharmacology and Experimental Therapeutics from Ref. [53].

sinus nodes disappear under those circumstances by impaired driving force for currents responsible for diastolic depolarisation. Unfortunately, voltage- or patch-clamp studies on single cells isolated from intact sinus nodes cannot easily explain these differences in intrinsic rate, because single cells are irregular [27].

3. Innervation and the autonomic balance

3.1. Innervation and receptor density

Papers on innervation of the sinus node report that ‘nerve supply is rich’ [54–56], but there is little detailed information available. The location of ganglion cells in or near the sinus node is species dependent [57]. There is inhomogeneity in innervation because vagal stimulation [58–62] and sympathetic stimulation [63,64] both cause shifts in the site of pacemaker dominance and activation pattern. There is also dispersion in receptor density, because addition of acetylcholine and adrenaline also increases heart rate. Table 1 (compiled from Refs. [74,75]) shows vagal predominance in the dog: the spontaneous heart rate in the instrumented conscious dog is lower (112 beats/min) than under combined muscarinic plus β-adrenoceptor blockade (160 beats/min) [74]. Also, in man vagal predominance results in a much lower resting heart rate than in the intrinsic heart rate shown by Jose and Collison [1].

Fig. 3. Cycle length of rabbit sinus node at normal Na+ concentration (100%) and normal Ca2+ concentration (2.2 mMol/l), at normal Na+ concentration (100%) and low Ca2+ concentration (1.1 mMol/l), at low Na+ concentration (50%) and normal Ca2+ concentration (2.2 mMol/l) and at low Na+ concentration (50%) and low Ca2+ concentration (1.1 mMol/l). Under all circumstances there is a large variability between individual sinus nodes despite identical experimental circumstances. However, if both the Ca2+ and the Na+ concentrations are low, this interindividual variability disappears and cycle length is about 420 ms in sinus nodes from all animals (n = 10). Reproduced with permission of the American Society for Pharmacology and Experimental Therapeutics from Ref. [53].
Determinants of the intrinsic heart rate in man

Cardio-accelerator fibres in the vagal nerves [76–81]. The mediators of this ‘non-muscarinic’ effect is probably a peptide factor [80,81].

Pacemaker shifts are relevant for the chronotropic response to changes in sympathetic (autonomic) tone [36]. The same amount of (nor)epinephrine produces little acceleration, when the acetylcholine concentration or vagal tone is higher [66,82,83]. In contrast, in the presence of a high noradrenaline concentration or a high sympathetic tone, the effect of acetylcholine is large. This phenomenon has been named ‘accentuated antagonism’ and has been explained by interaction between the two limbs of the autonomic nervous system at the pre- and postjunctional sites [82,84]. Although this explanation seems valid, it should be noted that at least the rabbit sinus node comprises areas with low, intermediate and high responsiveness to both transmitters of the autonomic nervous system [67]. A high vagal tone shifts pacemaker dominance to areas with low responsiveness to both transmitters, whereas a high sympathetic tone shifts pacemaker dominance to areas with high responsiveness to both transmitters. It has been observed in dogs that bilateral vagal stimulation results in lower heart rate in combination with stellate ganglion stimulation than in combination with noradrenaline infusion [85]. Although a prejunctional interaction may explain this observation, there certainly is an alternative explanation. High vagal tone will shift the pacemaker to an area with lowest innervation. Such an area may still accelerate in response to circulating catecholamines, but not or much less to sympathetic stimulation, simply because there is little innervation of that particular area. Thus, in addition to pre- or post-junctional interaction, pacemaker shifts certainly in part explain the ‘accentuated antagonism’. We emphasise the intricate mechanism by which the sinus node responds to catecholamines, because heart rate often is taken as an index for general sympathetic or autonomic input to the whole heart. However, even if heart rate is kept constant, although exerted by different combinations of vagal and sympathetic input, it has been demonstrated that refractoriness in atria and ventricles may change substantially [86] (see also [87–89]).

4. Concluding remarks

Jose and Collison have demonstrated that the intrinsic heart rate decreases with age in man [1]. Unfortunately, it is not completely certain that the intrinsic heart rate as determined by Jose and Collison [1] really reflects an intrinsic characteristic of the heart. Two issues remain to be settled: (i) The observed decrease in heart rate with age in the combined presence of propranolol and atropine may also be caused by a change in α-adrenoceptor density in the sinus node area. (ii) The non-muscarinic effects of vagal stimulation may change during aging. As long as

The effect of pharmacological autonomic blockade is complicated. The Table 1 shows differences between the effects of combined muscarinic blockade and β-adrenoceptor blockade and vagotomy and β-adrenoceptor blockade. Obviously, in the conscious dog [74] the intrinsic heart rate is much higher during (complete?) pharmacological blockade (160 beats/ min) than during the combination of vagotomy and β-adrenoceptor blockade (95 beats/ min). This discrepancy may be due to the presence of

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Heart rate (beats/min)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>112</td>
<td>[74]</td>
</tr>
<tr>
<td>Vagotomy</td>
<td>128</td>
<td>[74]</td>
</tr>
<tr>
<td>β-adrenoceptor blockade</td>
<td>77</td>
<td>[74]</td>
</tr>
<tr>
<td>β-adrenoceptor + muscarinic blockade</td>
<td>160</td>
<td>[74]</td>
</tr>
<tr>
<td>β-adrenoceptor blockade + vagotomy</td>
<td>95</td>
<td>[74]</td>
</tr>
<tr>
<td>Isolated right atrium</td>
<td>127</td>
<td>[75]</td>
</tr>
</tbody>
</table>

*Compiled from Ref. [74] (‘spontaneous and autonomic blockade’) and Ref. [75] (‘isolated sinus node’). The isolated sinus node data were from pups [75].

Fig. 4. Heart rate in normal conscious rabbits (‘in vivo’) and in rabbits with deafferentiated baroreceptors in the carotic and aortic sinuses (‘deafferentiated’). The isolated right atrium has a lower rate and displays hardly beat to beat variability (‘right atrium’). The in vivo heart rate is faster indicating a prevailing sympathetic tone. A vagal tone is nevertheless present, because deafferentiation causes a further increase in heart rate. Compiled from Ref. [52].
these two issues have not been settled, changes in ‘intrinsic heart rate’ between control groups of patients and groups of patients with heart disease cannot unequivocally be ascribed to an intrinsic property of the heart (the sinus node), even if there is no age difference between the groups.

References


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