congenital heart disease. In 22/25 patients, BNP plasma level was normal according to age- and sex-matched controls (between 5 and 21 pg/mL), despite an invasive pressure gradient of up to 105 mmHg, a left ventricular systolic pressure of up to 220 mmHg, and a markedly increased left ventricular hypertrophy in several patients. Plasma BNP was slightly increased when compared with healthy controls in 2/25 patients (22 and 40 pg/mL, 14.5- and 13.8-year-old boys, peak-to-peak gradient 90 and 65 mmHg, respectively). Only in one case, we found a markedly increased plasma BNP level of 195 pg/mL (age- and sex-matched controls: 8.5 ± 7.5 pg/mL). This 7-week-old girl had aortic valve stenosis with a systolic invasive pressure gradient of 40 mmHg, without left ventricular hypertrophy, but with an increased left ventricular diastolic and systolic dimension (shortening fraction 30%).

We could not find any correlation between plasma BNP level and invasive peak-to-peak gradient or maximal aortic velocity assessed by continuous-wave Doppler echocardiography. To our experience, in children and adolescence, it would be harmful to wait for elevated BNP levels before initiating interventional or surgical treatment.

We estimate that elevated plasma levels of BNP do not correlate to the severity of aortic valve obstruction but reflect the occurrence and the degree of left ventricular dysfunction. Although we cannot exclude that plasma NT-proBNP and BNP show different patterns, the similar results for BNP and NT-proBNP in adults with aortic stenosis reported by Gerber et al. do not support this suspicion. More probably, the differences between paediatric and adult patients may be explained by the greater possibility for compensation of left ventricular function in younger patients than in elderly patients with aortic stenosis.

These differences according to age should be taken into account. We believe, the younger the patient, the less reliable is the measurement of natriuretic peptides for monitoring patients with aortic valve stenosis.

References


Plasma levels of B-type natriuretic peptide in children and adolescents with aortic valve stenosis: reply

We thank Drs Koch and Singer for reporting their interesting findings on B-type natriuretic peptide (BNP) values in children and adolescents with aortic valve stenosis. These very important data indicating a limitation of BNP and probably also NT-proBNP assessment to evaluate severity of aortic valve disease in children and young adults.

In our study, only adult patients with calcifying aortic valve disease were included. For these patients, an elevation of BNP and NT-proBNP related to severity of aortic valve disease or functional status has been consistently shown in several published studies including at least 750 patients. Thus, it has to be assumed that the different release pattern in children with aortic stenosis is related to differences in pathophysiology-like differences in left ventricular myocardial adaptation and compensation.

Therefore, our results cannot be extrapolated to a paediatric population. The diagnostic value of BNP and NT-proBNP in these patients has to be assessed in separate studies.

Impact of ventricular response irregularity in patients with atrial fibrillation and heart failure

We read the recent article by Melenovsky et al., concerning functional impact of ventricular response irregularity in patients with atrial fibrillation (AF) and heart failure and found it interesting. The authors found that irregular biventricular pacing produced an impairment in left ventricular (LV) function in comparison with regular pacing when the mean rate was 120 b.p.m., but not when the mean rate was 80 b.p.m. The results of the study highlight that rate control rather than regularization should be the primary aim in these patients.

We would like to point out an important aspect in the interpretation of these findings. A correct evaluation of the effect of heart rate on differences in LV performance between regular and irregular pacing requires algorithms of irregular stimulation to produce comparable degrees of RR interval variability and/or irregularity at different mean rates. This condition is a major issue for such an analysis, as it allows us to rule out the hypothesis that the detrimental changes in cardiac function observed during irregular vs. regular pacing at high rates, but not at normal rates, may derive from different RR variability or irregularity indices, and not from the increase in mean ventricular rate itself. Unfortunately, a comparison of such parameters between the ventricular cycle series used to stimulate irregularly at 80 and 120 b.p.m. was not reported in the text. The authors used computer-generated irregular sequences of RR intervals that followed the discrete Poisson distribution—a well-known probability function that accurately describes the probabilistic behaviour of the ventricular response to AF. However, a Poisson-distributed series of ventricular cycles may be characterized by consistently different degrees of RR interval variability, depending on the mean cycle length, the histogram bar width, and the minimal RR interval under which the probability reduces to zero, i.e. the absolute refractory period of the atrio-ventricular node. Beat-to-beat variability and RR irregularity indices may also vary significantly, even in distributions with similar mean values and standard deviations.

These considerations raise the problem of defining the concept of ‘comparable’ degrees of variability and/or irregularity at

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different mean rates, as several indices have been previously proposed to analyse the dynamics of ventricular response to AF.\textsuperscript{2–4} Moreover, it should be taken into account that in patients with AF most of these indices show a positive association with mean ventricular cycle length.\textsuperscript{7} From this point of view, in order to better analyse the effect of heart rate on the differences in cardiac function between regular and irregular ventricular pacing, it may be appropriate to generate sequences of RR intervals with different mean rate but similar rate-adjusted parameters of both variability and irregularity. However, it might also be interesting to evaluate the haemodynamic effect of sequences characterized by variable degrees of RR variability and irregularity, in order to explore the relative role of each index, and its interaction with mean heart rate, in affecting cardiac function. We believe that future analyses investigating these issues may further reinforce the message of this study, and clarify intriguing aspects of LV haemodynamic response to AF.

References


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Impact of ventricular response irregularity in patients with atrial fibrillation and heart failure: reply

We appreciate the interest of Ballo et al. in our study and their thoughtful comments. Their major concern was that the observed haemodynamic differences between regular and irregular pacing at two different levels of heart rate might have been confounded by differences in R-R interval variability at the two rates. We appreciate how this concern might arise given the lack of full details regarding the pacing sequence we used to simulate atrial fibrillation. However, as explained in detail here, we believe this concern is not warranted.

We used a random number generator to derive an R-R interval sequence at a mean rate of 80, which yielded an event histogram following a Poisson distribution. As noted, this is typical of R-R interval histograms that approximate naturally occurring atrial fibrillation.\textsuperscript{1} For studies at the faster rate, we used the identical random sequence of R-R intervals, but shortened each interval by one-third, taking into account dependency of heart-rate variability on prevailing mean heart rate.\textsuperscript{2,3} Thus, the coefficient of variation (COV = SD/mean x 100), was identical at both mean rates (25.6%). This mirrors measured data from patients with atrial fibrillation in whom adrenergic or anticholinergic medications were used to vary heart rate (48, 60, and 90 b.p.m.), yet the COV of the R-R intervals remained essentially constant at ~23% for each rate.\textsuperscript{2} In addition, we used the identical ‘random’ time-sequence of R-R intervals at both rates, so the temporal course of intervals was reproduced in each patient at each rate. We regret that these details were not provided in the manuscript.

We agree that it would be interesting to investigate the haemodynamic consequences of different degrees of R-R variability and irregularity (entropy), particularly in the setting of an animal model. However, in an invasive study of severely ill human subjects, we limited our efforts to the most contrasting conditions—the categorical comparison between completely regular and irregular pacing sequences with a distribution that resembles real-life atrial fibrillation.

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