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Hypothesis

Rats with Postinfarction Heart Failure: Effects of Propranolol Therapy on Intracellular Calcium Regulation and Left Ventricular Function

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Abstract

Patients with heart failure may live longer if they receive chronic treatment with beta-adrenergic blocking medications. Unresolved are the mechanisms underlying the beneficial effects and if they may be applied to ischemic heart failure. Rats (*n* = 28) underwent echocardiographic-Doppler exams one and six weeks following a simulated operation or myocardial infarction (MI). After the first echocardiography, rats were randomized to either no therapy or 500 mg/l of propranolol in their drinking water. The noninfected left ventricular (LV) papillary muscles were used to record isometric contractions and intracellular Ca transients simultaneously.

Untreated MI rats had a restrictive LV diastolic filling pattern, decreased systolic function (13% ± 2%), and significant LV dilatation (10.6 ± 0.4 mm *vs*. 8.9 ± 0.3 mm, MI *vs*. control). The LV chamber diameters of the propranolol-treated MI rats were 10.6 ± 0.5 mm, and systolic performance (13% ± 2%). Higher LV end-diastolic pressures (27 ± 2 mmHg *vs*. 20 ± 3 mmHg) and a more constrained LV diastolic filling pattern (increased ratio of early to late filling velocities and faster E wave deceleration rate) were seen in the propranolol-treated animals. Papillary muscle contractility in untreated MI rats was lower (1.6 ± 0.3 g mm²). Furthermore, the inotropic response to isoproterenol was attenuated, and Ca transients were extended. During isoproterenol stimulation, beta-adrenergic blocking administration had no effect on force development (1.6 ± 0.3 g mm²) or the length of Ca transients.

Rats with postinfarction heart failure receiving chronic propranolol treatment did not have improvements in systolic function or LV remodeling. Propranolol exacerbated LV diastolic pressures and filling patterns. Additionally, there was no discernible improvement in intracellular contractility following treatment, Calcium control, or beta-adrenergic sensitivity in the myocardium that is not infarcted).

More Information

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Introduction

The use of beta-adrenergic blocking medications to treat patients with left ventricular (LV) dysfunction is becoming more and more popular [1]. Nonetheless, there are still a number of contentious issues around the usage of beta-blockers in this situation. According to certain studies [2-4], individuals with ischemic illness as the cause of their heart failure may benefit less from long-term beta blocking than do patients without this condition. According to other research, these medications may help individuals with heart failure who have nonischemic as well as ischemic etiologies [5]. Numerous elements of According to Bohm, et al. [6] and Bristow, et al. [7], ischemic and idiopathic dilated cardiomyopathy appear to affect the beta-adrenergic signal transduction pathway differently. According to Woodley, et al. (1991), these differences may be the cause of the inconsistent effects of beta-blocking in patients with these different kinds of cardiac muscle diseases. Second, although numerous investigations (Bristow, et al. 1996; The CIBIS investigators, 1994) indicate that beta-blocking improves the LV ejection fraction, it is unclear if contractility is improved at the cellular or tissue level (Wagner, et al. 1997). Lastly, conflicting evidence exists on the possibility that beta-blocking enhances left ventricular diastolic function [8]. Given the ambiguity surrounding efficacy (Consider relocating the justification for using propranolol as a beta blocker to page 2, preceding the "methods" section, to provide a clearer introduction

to its significance in the study.)Considering the potential processes behind the beneficial effects of beta-blocking in post-infarction left ventricular failure, we set out to address these issues in our investigation. Does long-term nonselective beta-adrenergic blockade in post-infarction heart failure: (1) lessen or reverse LV remodeling? (2) change how LV diastolic and systolic dysfunction develop. and (3) shield the noninfarcted myocardium from anomalies in excitation-contraction coupling. Research on animals can be useful in determining the mechanisms underlying pharmacological effects since, compared to human volunteers in clinical trials, animals usually produce a far more homogeneous sample. Furthermore, studies conducted on animals offer the chance to acquire cardiac tissue and do follow-up investigations. As we've already shown, it's feasible and reproducible to the ability to measure left ventricular shape and function in rats after a massive anterior MI using transthoracic echocardiography [9]. This technique's noninvasiveness makes it perfect for these studies since it enables longitudinal evaluation of LV shape and function both before and after treatment is started. In the current investigation, we integrated ex vivo evaluation of myocardial contractility and excitation-contraction coupling in noninfected myocardium with echocardiographic studies. According to our research, five weeks of propranolol therapy for post-infarction heart failure appears to have no effect on LV remodeling or the advancement of systolic dysfunction, deteriorate diastolic function, have no discernible effect on the prolongation of intracellular Ca transients, and have no beneficial effect on beta-adrenergic signaling in the surviving myocardium.

Methods

Model of ischemic heart failure

Every study included in this publication was carried out in compliance with American Physiological Society rules. As previously reported (n = 14), anterior myocardial infarction (MI) was induced in male Sprague-Dawley rats (age roughly 12 weeks, weight 250 ± 300 g). Despite undergoing the same procedure, 14 sham-operated rats did not get a myocardial infarction. Since these animals experience progressive LV remodeling and contractile dysfunction as a result of heart failure, we focused on rats with large infarctions (440% LV circumference). One week following surgery, rats with MI or sham surgery were randomized to receive either no treatment at all or a chronic propranolol treatment. It has previously been demonstrated that in this type of heart failure, the dosage of propranolol (500 mg/l in drinking water) produces clinically significant beta blockage. (Gay and others, 1990). For a total of five weeks—six weeks following surgery—propranolol or no therapy was administered. To avoid potential adverse effects of earlier beta-blocker administration in animals with compromised LV function, treatment was initiated one-week post-surgery.

Echocardiography investigations

Rats were anesthetized with ketamine HCl (Parke Davis, Morris Plains, NJ, U.S.A.) at a dose of 50 mg kg71 and xylazine (Lloyd laboratories, Shenandoah, IA, U.S.A.) at a dose of 10 mg kg71 intraperitoneally one week following MI or sham surgery, just prior to the start of propranolol or no treatment. The echocardiographic procedure was carried out as previously described [9,10]. Using the M mode strip chart recordings, measurements of the LV internal dimensions and anterior and posterior wall thickness (end-diastolic and end-systolic) were taken from at least three consecutive cardiac cycles. Mitral flow was measured using pulsed-wave Doppler spectra from an apical four-chamber view. The sample volume was positioned at the tips of the mitral leaflets and adjusted to the location where the flow pattern was greatest and the velocity was thin-film.

"By integrating the pulsed-wave Doppler spectra obtained in the LV outflow tract, the stroke volume was determined. For every metric measured, the mean of a minimum of three consecutive cardiac cycles was used. 18 ± 24 hours before the initial echocardiography (6 weeks following MI or fake surgery), propranolol was stopped. A 2 Fr. micromanometer-tipped catheter (Millar Inst., Houston, TX, U.S.A.) calibrated at 37 °C was retrogradely introduced into the left ventricle via the right carotid artery after the echocardiographic investigation. Using a differentiating circuit, the electronic signal was run to determine the first derivative of pressure (dP/dt).

Isometric muscular function the heart was quickly removed after the hemodynamic readings were taken. In an oxygen-filled dissecting environment, the noninfarcted posterior papillary muscle was dissected free, and a spring clip was used to hold onto the muscular end. There was no obvious indication of infarction in any of the muscles. Previous research has demonstrated that although varied interstitial fibrosis is evident 6 ± 9 weeks after MI, the posterior papillary muscles do not exhibit significant scar tissue on histologic inspection (Litwin, et al. 1991; Warner, et al. 1992). The tendinous end of the muscle was suspended vertically from an isometric force transducer (MBL 341 Sensotech Inst, Columbus, OH, U.S.A.) and knotted with a 6 ± 0 silk suture. The modified Krebs ± Henseleit solution, comprising the following components (mmol l^{-1}): NaCl 120, KCl 5.9, dextrose 11, $NaHCO_3$ 25, NaH_2PO_4 1.2, $MgCl_2$ 1.2, and $CaCl_2$ 1.0, was added to a 50 ml tissue bath before the muscle was placed in it. The bathroom was kept up, maintained at a steady 30 °C, and bubbled with 95% oxygen and 5% carbon dioxide. An isometric contraction of the muscle was induced at 0.33 Hz by means of a punctate platinum electrode positioned at the muscle's base. Square wave pulses lasting five milliseconds were applied at a voltage that was roughly 10% above the threshold. The length of the muscle at which the greatest amount of tension developed was stretched. Every study ended with a measurement of muscle length. After that, the muscle was weighed and gently

blotted dry. The cross-sectional area of the papillary muscle was then computed using the assumption that the muscle had a cylindrical shape and a specific gravity of 1.05: cross-sectional area ≈ muscle weight = 1.05^3 = muscle length."

Measurements of aequorin signals using a method previously described

Aequorin (bought from J.R. Blinks, Friday Harbor, WA, U.S.A.) was loaded (Litwin & Morgan, 1992). Dr. John R. Blinks' light-collecting device was used to measure the aequorin signal once background light levels had dropped to a stable baseline. The force transducer and a photon counter (C10, Thorn EMI Gencom Inc, Fair®eld, NJ, U.S.A.) connected to the photomultiplier tube were used to simultaneously record light and isometric strain. The data from 20 ± 40 steady-state light signals and isometric twitches were averaged (#4562 Nicolet, Madison, WI, U.S.A.) to increase the signal-to-noise ratio. Isoproterenol-induced inotropic reactions following completion of baseline measurements, isometric tension and aequorin signals were recorded while the beta-adrenergic agonist isoproterenol was administered to achieve cumulative concentrations of 1079 ± 1076 mol l71, isoproterenol HCl (Sigma Chemical Co., St. Louis, MO, U.S.A.) was dissolved in distilled water and added to the bath. Following each administration of isoproterenol, the reaction peaked 5 ± 10 min later, at which point light signals and isometric contractions were recorded.

Study on pathologies

Following the excision of the heart's papillary muscle, the ventricles' atria were cut off, and the septum left ventricle, and right ventricle were all separated and weighed. After that, the tissues were immersed in 10% butyrate formalin. Every heart was sectioned four times, from the apex to the base, and readyed for standard histology. Masson's trichrome was used to stain thin slices from each level. By calculating the percentage of the endocardial circumference that was replaced by scar tissue, the infarct size was determined in the section that corresponded to the midventricular short-axis echocardiogram. Figures the format for all data is mean+s.e.mean. Week 1 and Week 6 intergroup comparisons were conducted using a factorial ANOVA and a post hoc analysis. When applicable, use Fisher's least protected significant difference test (Statview 4.01, Abacus Concepts, Berkeley, CA, U.S.A.) for multiple comparisons. It was determined that a probability of 50.05 was significant. With n = 7 rats in each group, we predicted that, given the variability observed in our prior investigations, we would have an 80% chance of identifying differences of about 30% in the LV diastolic dimension, the E wave deceleration rate, or the myocardial contractility (peak rate of tension rise). Just the post hoc comparisons of each group versus the untreated sham and propranolol MI versus the untreated MI are shown for clarity's sake.

Discussion

We discovered that significant left ventricular dilatation, regional and global systolic dysfunction, aberrant diastolic fillings, and contractile dysfunction in isolated muscle preparations were the hallmarks of ischemic heart failure in rats.

In this model of heart failure, beta-adrenergic inhibition had no effect on systolic dysfunction or LV enlargement development. Rather, the LV diastolic filling anomalies were slightly aggravated and LV end-diastolic pressures were increased even more with active treatment. The papillary muscles' isometric contractility did not significantly improve as a result of the treatment, despite a minor decrease in the duration to peak tension and the Ca transient (P = NS). Additionally, inotropic responsiveness to beta-adrenergic stimulation was not restored by propranolol therapy. Therefore, in this model of postinfarction heart failure, persistent nonselective beta-adrenergic receptor blockage seems to have relatively few beneficial effects and may even exacerbate diastolic problems. Treatment with beta-adrenergic blocking medications, both acute and long-term, has been linked to increased survival in individuals who have just suffered an MI [11]. There could be multiple processes involved in these effects. Acute beta-blockers may reduce the size of the infarct. Reductions in sudden cardiac death appear to be a contributing factor to the improvement observed with beta-blocking [11]. Lastly, it can be crucial to avoid further MI or other ischemic episodes (Roberts, et al. 1991). The purpose of our study was not to assess the effects on the size of infarcts or long-term survival. Our main focus was on the effectiveness of beta-blocking in addressing structural or functional problems in patients with established heart failure. The majority of arrhythmic deaths in this model happen within the first 24 hours after MI. and after more than 30 days, late deaths usually start to happen (Opitz, et al. 1995; Pfeer, et al. 1985a). We did not anticipate a treatment-associated decrease in mortality because therapy was given during a time when mortality in the untreated MI mice was predicted to be very low. In our model, recurrent or persistent ischemia did not pose a problem since the coronary circulation remains normal outside of the ligation site. Our study design precluded the demonstration of beta blockade's anti-ischaemic and antiarrhythmic effects, but it did lead us to conjecture that long-term propranolol administration would be linked to enhancements in left ventricular remodeling and hemodynamics. Additionally, we proposed that improvements in excitation-contraction coupling and myocardial function could account for such positive effects.In this heart failure model, we could not find much evidence that propranolol had any beneficial effects on left ventricular, myocardial, or cellular function. The increasing amount of research on the beneficial effects of beta blockage makes it crucial to carefully assess the significance of our findings. First, it's likely that the

power of our investigation was insufficient to identify subtle but meaningful improvements in the shape or function of the left ventricle. This appears improbable given that the treated animals' function appeared to be declining if there was any trend at all. Additionally, we have previously demonstrated the significant benefits of long-term captopril-induced inhibition of the angiotensin-converting enzyme in a similar number of participants and the same cardiac failure model (Litwin & Morgan, 1992) [10]. According to those investigations, myocardial function, intracellular calcium modulation, beta-adrenergic responsiveness, and LV filling patterns all significantly improved after 5 weeks of captopril administration (Litwin & Morgan, 1992) [10]. Second, according to Steeds and Channer (1997) and the CIBIS investigators (1994), beta-blockers may be helpful in treating certain types of heart failure but ineffective in treating others. According to certain research, patients with idiopathic dilated cardiopathy appear to benefit from treatment more than those with ischemic heart disease in terms of LV systolic function (Doherty, et al. 1992; Woodley, et al. 1991; Bristow, et al. 1996; 1991). [7] This finding could have a lifelong myocyte loss consequence from MI in the infarcted region. Even during beneficial treatment, the quantity of viable myocardium that remains may not be sufficient to demonstrate a significant improvement in overall left ventricular function. In contrast, people with idiopathic dilated cardiomyopathy may have hearts with a higher absolute number of viable myocytes. The prognosis for patients with ischemic cardiomyopathy is significantly poorer than for those with idiopathic cardiomyopathy, which may be explained by the irreversible nature of ischemic damage [12]. Third, the advantages of beta-blockers might apply only to particular drugs. The receptor selectivity of beta-blockers varies greatly (beta Vasodilatory effects, duration of action, inherent sympathomimetic activity, and beta 1 *vs.* beta 2 receptor subtypes are among the factors to consider. Different drugs have been employed in different clinical studies, with different patient populations involved, different end objectives, and different treatment durations. As a result, it is somewhat challenging to directly compare the results of these investigations. Few published studies directly comparing the effects of various medications on heart failure treatment are currently available. In a rat model of ischemia and reperfusion injury, it has been proposed that carvedilol is more effective than propranolol in reducing the size of infarcts; however, this comparison was made indirectly [13]. Gilbert, et al. discovered that carvedilol, a vasodilating beta-blocker, improved functional classification more and tended to outperform metoprolol in improving the left ventricular ejection fraction [14]. Carvedilol may be particularly effective among the several beta-blockers due to recent research [5] demonstrating its beneficial effects in patients with ischemic heart failure. Consequently, rather than being able to block beta-adrenergic receptors, carvedilol's effects may also be connected to its vasodilating, antioxidant, or antineutrophil effects [13,15]. According to Gilbert, et al. [14], some researchers think that blocking the beta-2 receptor subtype is significant and could help to explain why some trials have found relatively little efficacy from highly beta-1 selective drugs. Remarkably, Carveilol does not increase beta-adrenergic receptor density, according to at least two publications [14,16]. Therefore, changes in membrane receptors are most likely unrelated to the drug's beneficial effects. It has been demonstrated that propranolol, a commonly used nonselective beta blocker, increases survival in individuals who have had a recent MI [11]. Furthermore, in this animal model of heart failure, propranolol has been demonstrated to increase beta-adrenergic receptor density (Warner, et al. 1992). Therefore, it appeared to be a suitable substance to investigate the comparatively unadulterated effects of beta-adrenergic receptor blockage. Cherng, et al. discovered, in line with our findings, that metoprolol did not significantly improve Myocardial infarction-prone rats (Cherng, et al., 1994). An additional factor to take into account is that beta-blockers have been included in every recent clinical trial along with angiotensin-converting enzyme inhibitors, diuretics, and dioxin regimens (Packer, et al., 1996). While beta-blockers without vasodilating effects are ineffective when taken alone, the combination of these medications may be beneficial. Fourth, the effectiveness of beta-blocker may vary depending on the species. It's plausible that people react to beta blockage but rats do not. There isn't any material that directly confirms or denies this theory. Nonetheless, in rats, propranolol blunts the chronotropic effects of isoproterenol, producing clinically significant suppression of beta receptor-mediated effects [17]. The shrew model of postinfarction heart failure bears many similarities to the human scenario. In this model, like in humans, angiotensin-converting enzyme inhibitors enhance survival and hemodynamics (Litwin & Morgan 1992; Pfeer et al., 1985b; Raya, et al. 1989). Similar to human findings, calcium channel blockers do not appear to have any beneficial effects on rats with MI [18]. Lastly, a wealth of evidence in this cardiac failure paradigm demonstrates sympathetic and neurohumoral activation (Schunkert, et al. 1993; Teerlink, et al. 1994) [19]. If the degeneration of function following ischemic left ventricular damage is directly caused by this overactivation of compensatory systems, beta blocking ought to be effective in rats as well as other animals. Lastly, The length and timing of therapy could be crucial. We believed that after one week from surgery, the animals would be stable enough to go through echocardiogram and be able to handle starting propranolol therapy. We were worried that in animals with quite acute heart failure, starting medication early could have negative effects. On the other hand, it's also conceivable that receiving treatment sooner may have been beneficial. Notably, LV filling, myocardial function, and intracellular calcium regulation are significantly improved when captopril medication is started at the same time point and maintained for the same amount of time (Litwin & Morgan, 1992) [10]. It's interesting to note that Hu et al. claimed that bisoprolol

medication started 14 days after MI was more beneficial than early treatment thirty minutes in the rat following MI [20]. The purpose of the treatment term in our investigation was to allow any potential beneficial effects to become apparent before the untreated rats died in a significant way. We might have noticed greater benefits if the treatment had lasted longer. According to Hall, et al. [21], some researchers have hypothesized that patients may experience an initial worsening of their symptoms and LV function, that LV function improvement may take months, and that normalization of LV geometry may not become apparent until after they have been taking beta-blockers for longer than a year. A certain length of treatment in a rat is not the same as the same length of treatment in a human. Using a normal life span of roughly three years, rats have faster biological processes than larger species. Consequently, five weeks of therapy equates to a noticeably longer course of treatment in people. And last, there's a chance that the propranolol dosage wasn't the best one. Potentially beneficial effects of the treatment may have been masked if the dose was either too high or too low. The 500 mg/l71 dose of drinking water was selected because previous research has demonstrated that in intact animals, it causes a slowing of the heart rate and a reduction in the chronotropic responsiveness to isoproterenol [17]. Additionally, it has been demonstrated that in this heart failure model, this dosage increases the density of beta-adrenergic receptors (Warner, et al. 1992). Given that the patient was Given that the animals exhibited worsening LV filling pressures and a more constricted diastolic filling pattern, it is doubtful that the dosage was insufficient. Higher doses of beta-blockers were said to have a more significant beneficial effect in certain clinical trials (Bristow, et al. 1996). Therefore, we don't think the dosage we used was excessive. Study constraints The study's possible drawbacks have been discussed previously. The applicable Creative Commons License regulates the restrictions of the echocardiographic approach in S.E. Litwin, et al. Propranolol in ischemic heart failure on Open Access papers; these have been previously addressed [9]. The use of papillary muscle preparations to evaluate cardiac function is controversial while being frequently used. Concerns like broken muscle endings, core hypoxia, and uneven loading of the Ca indicator are all legitimate issues. Prior research on these topics has been done in-depth (Litwin, et al. 1991; Litwin & Morgan 1992). Papillary muscle investigations have several drawbacks, but they have also yielded a wealth of information regarding the functioning of the heart. While the outcomes of the majority of the present studies are "negative" in that no therapeutic benefit was shown; however, this does not make the findings any less significant than those of a "positive" study. The true effects of a particular treatment in unselected patients may be difficult to determine due to the potential for clinical trials to selectively report favorable findings. Patients who were unable to tolerate the initial doses of beta-blockers were typically omitted from trials (Packer, et al. 1996) [5]. As a result, there may be a bias in the published evidence to support therapeutic efficacy. Furthermore, practically every patient who signed up for the clinical trials had been stabilized on angiotensin-converting enzyme inhibitors before the beta blocker establishment. Given that there appears to be a synergistic effect between various pharmacological groups, this could be significant (Exner, et al. 1999). Our findings do not rule out the possibility of beta blockade's beneficial effects in individuals with ischemic heart failure; yet, we did not find much evidence of a beta-adrenergic blockade-related myocardial protective effect.

Outcomes

Effects of propranolol and MI on hemodynamics and cardiac chamber weights *40% of surgical deaths occurred in the first 24 hours. Neither the treatment period nor the echocardiography or hemodynamic assessments resulted in any animals dying. Untreated MI rats developed significant right ventricular hypertrophy, a symptom of prolonged LV dysfunction. The hemodynamic irregularities matched those previously documented in rats suffering from heart failure following an infarction (Litwin & Morgan, 1992; Peer, et al. 1979). Rats with significant MI in particular had raised LV end-diastolic pressure, lowered maximal and minimal LV dP/dt, and decreased LV systolic pressure. Histologically confirmed infarct size did not differ between propranolol-treated and untreated MI animals Given that propranolol was not administered until after the infarctions occurred. Rats with MI treated with propranolol weighed significantly less than the sham-operated rats and somewhat less than the untreated MI animals. Compared to the untreated MI rats, propranolol did not affect the development of right ventricular hypertrophy or the ratio of LV weight to body weight. The four groups of rats had identical heart rates. Since data were taken 18 ± 24 hours following treatment termination, this was expected. When compared to the corresponding untreated groups, propranolol marginally decreased + and 7dP/dt in the sham and MI groups When propranolol was administered to MI rats, their LV end-diastolic pressure was much higher than when the rats were not treated. Effects of propranolol on systolic function and post-infarction LV remodeling As we've demonstrated before, After transmural anterior MI, echocardiographic measurements showed significant left ventricular remodeling [9,10]. Propranolol therapy had no significant effect on post-infarction left ventricular remodeling. Significant left ventricular systolic dysfunction was also linked to MI. Before starting propranolol treatment, LV fractional shortening was similarly decreased in the two groups of infarcted rats. After five weeks, the two metrics continued to drop in both treated and untreated rats. At the end of the trial, there was no difference in fractional shortening between the propranolol-treated and untreated MI rats. When compared to the untreated group (P = NS), the propranolol-treated MI rats exhibited a tendency towards better systolic thickening of the noninfected posterior wall.

Conclusion

A model of postinfarction heart failure showed that long-term propranolol administration was linked to greater LV filling pressures, lower LV dP/dt, and a more constrained LV filling pattern, but it did not significantly change postinfarction left ventricular remodeling. Treatment had no effect on basal contractility or inotropic responsiveness to isoproterenol in the noninfected myocardium. We did not look at survival or potential antiarrhythmic effects of propranolol therapy in our study. Nevertheless, there doesn't appear to be much of a contractile or hemodynamic improvement in this model. These findings imply that a rigorous assessment of beta-blockers needs to be done in order to ascertain the following: (1) which patient subgroups with LV dysfunction may benefit the most; (2) which drugs are the most effective; and (3) what the secondary effects of beta blocking are (4) Is the concurrent administration of vasodilating agents important in creating beneficial effects during long-term beta-adrenergic blockade agents (e.g., antioxidant activity or alpha blockade) important.

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