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ORIGINAL ARTICLE

The impact of antiarrhythmics on human pulmonary arteries: *Ex vivo* characterization

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Abstract

Background and Aim: The safety and efficacy of the antiarrhythmic agents, amiodarone, and digoxin, in patients with pulmonary hypertension (PH), is not described well in the literature, although their use is common practice. Our study aims to investigate the effect of these drugs on pulmonary arteries (PA) which may have implications for their use in patients with PH.
Methods: Human PAs were obtained from consenting patients undergoing lobectomies. Arterials rings (n=40 from ten patients) were dissected form the tissue and mounted onto a multiwire myograph. The rings were preconstricted using prostaglandin F2α before the addition of additive dilutions of amiodarone and digoxin. Finally, the reagents were washed out and the arterial rings' viability was confirmed using acetylcholine and potassium chloride.
Results: Amiodarone had a slightly vasodilatory effect on the arterial rings, whereas digoxin had a relatively neutral effect. Amiodarone caused the greatest vasodilatory response at 100 μM with an active tension of −0.494 gram force with an EC_{50} of 9.42 μM. Digoxin produced no significant vasodilatory or vasoconstrictive response.
Conclusions: This study demonstrated the *ex vivo* effects of amiodarone and digoxin on human pulmonary arterial tension. The results of the study showed that neither amiodarone nor digoxin had any vasoconstrictive effects. Amiodarone also exhibited vasodilatory properties and, therefore, may be used preferentially as it could help reduce the impact of PH. However, more studies need to be conducted before we can confirm the safety of these drugs.
Relevance for Patients: The ambivalence surrounding treatment of postoperative arrhythmias in patients with PH results is a significant disparity between individual cases. Our study takes the first step in elucidating, in which drugs may be a safer treatment for patients with the aim to resolve the doubts clinicians may have about using these treatments. The principal goal of our work is to ensure that we are providing patients with the most effective and, more importantly, safest treatment.

1. Introduction

Pulmonary hypertension (PH) has a wide range of implications in patients undergoing surgery with increased perioperative morbidity and mortality. These are especially pronounced when there are other perioperative complications such as post-operative arrhythmias (POA). The focus of our research is to study the effects of antiarrhythmic drugs (AADs) amiodarone and digoxin on human pulmonary arteries (PAs) and evaluate which may be a safer option in patients with PH.

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1.1. POA and concomitant PH

POAs are a well-known and common complication following cardiac surgery. The most common of these POAs is post-operative atrial fibrillation (POAF) with an incidence of up to 50% following cardiac surgical procedures [1] and up to 60% in complex procedures such as combined coronary artery bypass graft and valve surgery [2].

PH and arrhythmias also have a relationship outside the realm of surgical complications. Studies have estimated incidence of atrial fibrillation (AF) up to 30% in patients with PH [3]. The pathogenesis, here, is thought to be related to the cardiac remodeling that occurs due to chronically elevated pressures in the heart chambers [4]. These structural changes in the atrial walls puts the heart at risk of developing AF [5]. This is similar to the process, whereby inflammation and trauma after surgery puts patients at increased risk of POAF and potentially indicates that patients with PH may be predisposed to developing POAF.

AF can pose a significant risk to patients with PH and is closely associated with clinical deterioration in patients. Cohort studies have shown that 82–97.5% of patients present with markers of worsening function, diminished right ventricular function or even corpulmonale [6-8]. The decline in ventricular function is often a sequelae of the decrease in cardiac output, irregular ventricular rhythm, ischemia, and hypotension that result from AF [9,10]. However, successful treatment and return to sinus rhythm showed almost complete reversal of these risks [10]. Therefore, reversal of the arrhythmia and maintenance of sinus rhythm is a key management goal in these patients.

Management of POAF involves a strategy of either rate control or rhythm control. Rate control involves slowing the heart rate using drugs such as beta-blockers, calcium channel blockers, and digoxin, whereas rhythm control uses AADs like amiodarone with the aim to restore sinus rhythm [11]. Studies that examined the comparative efficacy of beta-blockers and amiodarone, which are the first-line agents for their respective strategies have shown that they are both effective drugs for the management of POAF [12,13]. However, there is a disparity in the evidence as to whether amiodarone reduces the length of hospital stay with older trials claiming that it does [14,15] and newer research showing that these differences are not clinically significant [11,13]. Digoxin, on the other hand, is only recommended by guidelines as a third-line rate limiting treatment for POAF [16].

In the context of PH, however, the treatment becomes significantly more complex as side effects of medication can lead to decompensated heart failure, especially in patient with pre-existing right ventricular dysfunction. Cor pulmonale in this context is usually caused by the negative chronotropic and inotropic effects of drugs, namely, beta-blocker and calcium channel blockers [5,17]. As opposed to the general population, patients with PH respond well to cardiac glycosides due to their favorable effects on ventricular contractility and cardiac output [18]. Digoxin is recommended by the European Society of Cardiology in PH patients with atrial arrhythmias [19].

Despite evidence depicting the benefits of amiodarone and digoxin in POAF, there are none that assess their safety and efficacy in PH [17]. Neither were we able to find any literature on the effects of AADs on pulmonary vasculature or the outcomes of patients with POAF and PH. Therefore, our trial focuses on assessing the *ex vivo* effects of amiodarone and digoxin on PA to determine if they have the potential to worsen PH and if either drug should be used preferentially.

2. Materials and Methods

2.1. Ethics

Ethical approval for the use of human pulmonary tissue was received form the Local Ethics and Research Committee (Research Ethics Committee approval reference: 15/NW/0808, HEY R&D reference: R1884). All patients who were included in our study were undergoing an elective pulmonary lobectomy at a tertiary care center. All patients were over the age of 18 years and were able to give informed consent. Any patient who did not suit these criteria was excluded from the study.

2.2. PA

Tissue from a total of 13 patients was used to run 52 trials during our study. PAs were isolated from healthy part of the resected lung while taking care to avoid tissue within a reasonable margin from diseased areas. Surrounding connective tissue and fat were also removed before PAs were dissected into small rings that were approximately 2–4 mm in internal diameter and 2–3 mm in width.

2.3. Experimental protocol

The PA rings are then immediately transferred to oxygenated Krebs-Henseleit solution until they could be mounted onto the DMT-620M multiwire myographs. The myograph chambers were, then, calibrated and the temperature was set at 37°C, the chambers aerated with 21% O_2: 5% CO_2, and the equipment is connected to the PC through an amplifier (Power Lab 8/35, AD Instruments) for continuous monitoring using data acquisition software (Lab Chart Pro Version 8.0). The software was also calibrated to recognize true values of the isometric tension using known weights.

Once calibrated the PA rings are mounted onto the myograph with the resting tension (RT) set to 1.61 gram force (gf), (1 gf is equivalent to 0.009807 newtons), as this was determined to be the optimal RT from previous experiments [20]. The vessels were allowed to equilibrate for 30 min to allow the tissue to settle in the experimental conditions. 11.21 μM of prostaglandin F2α (PGF2α) (EC_{80} as determined by previous experiments [21]) was then added to pre-constrict the vessels and mimic conditions of PH. Once the contraction reached a plateau, cumulative dilutions of amiodarone and digoxin were added in an additive sequence, that is, if the first concentration was 1 nM, 2 nM was added to make the new concentration of 3 nM. Each subsequent dose was added once the effect of the previous dose had reached a plateau.

After the final dose reached a plateau, the vessels were washed for 30 min to remove any drug residue before testing the vessel viability. 40 mM potassium chloride (KCl) (EC_{80} as determined by previous experiments [21]) was then added to check the

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contractility of PA rings and 1 μM acetylcholine (ACh) was used to test the integrity of the vessel endothelium. If there is no contraction, this may mean that the tissue is dead, and the results are not usable. Any vessels that did not react to the KCl and ACh were excluded from the results analysis. The sample traces (Figure 1) show the raw data recorded by Lab Chart that is used for the analysis. From the 52 trials that were conducted, 40 were used in the results analysis (20 samples each drug).

2.4. Drugs

Amiodarone is a Class III AAD that is predominantly used to treat ventricular arrhythmias. It also exhibits characteristics from antiarrhythmic Classes Ia, II, and IV. It works primarily by prolonging Phase 3 of the myocardial action potential [17]. It is also known to cause coronary and peripheral artery vasodilation through its adrenergic effects [22]. This could mean that it has a potential to help in pulmonary arterial vasodilation.

Digoxin is a cardiac glycoside that works by inhibiting the Na^+/K^+ ATPase on the myocardial cell membrane [23] to increase intracellular sodium and calcium ions which produce the clinically observed increase in myocardial contractility and cardiac output [17]. Digoxin's benefits in congestive heart failure has also been linked to its effects on circulatory congestion in addition to its positive inotropic effects [18]. This could potentially mean that it could have a role in relieving pulmonary arterial pressures in PH patients.

3. Results

The results were calculated as the active tension in response to every dose of drug added. Active tension was defined as the difference between the maximum tension under PGF2α and the tension in response to a specific drug dose. The active tension (y-axis) was plotted against the logarithmic concentrations (x-axis) of amiodarone and digoxin to construct the dose-response curves, Figures 2 and 3, respectively.

Every PA ring sample showed some vasodilatory response to amiodarone and the maximum vasodilation was seen at 100 μM. At concentrations above 100 μM, the vasodilatory effect of amiodarone seemed to be diminished. The EC_{50}, that is, the concentration that produced 50% of the maximum response, was calculated using the GraphPad Prism 9 software. The EC_{50} for amiodarone was calculated to be 9.42 μM, CI 95% (6.44–14.9 μM).

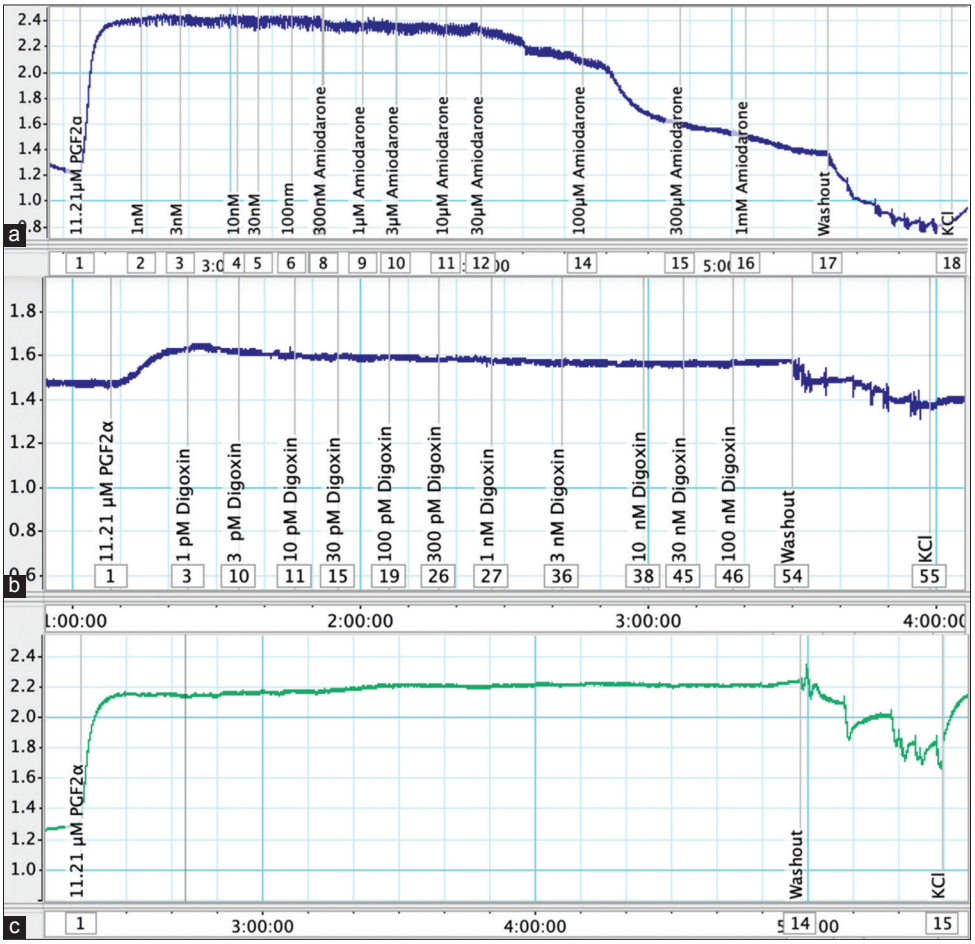

Figure 1. Sample traces of amiodarone (a), digoxin (b), and control (c) recorded on the PC using the Lab Chart Software. X-axis shows the time elapsed in hours and y-axis shows the tension of the vessel in gf. Boxed numerical values are label numbers for events during experiments and can be ignored.

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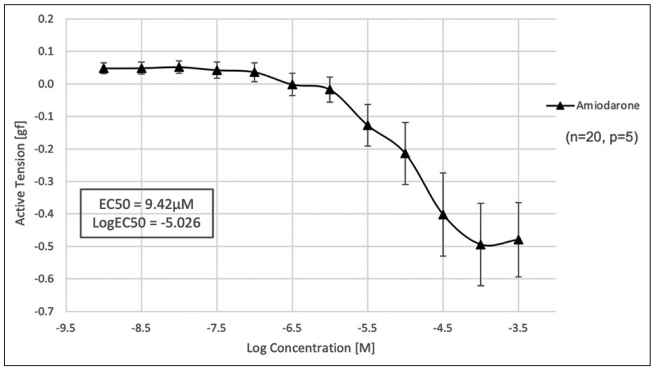

Figure 2. Dose-response curve for amiodarone. The active tension (y-axis) is plotted against the log concentrations (x-axis). The maximum response was noted at 100 μM with EC_{50} at 9.42 μM. N is number of samples and P is number of patients from who tissue was collected.

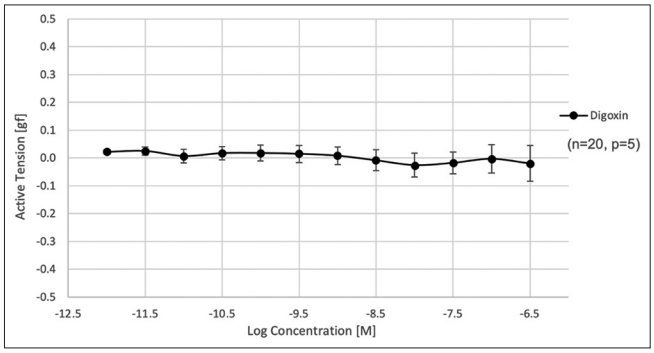

Figure 3. Dose-response curve for digoxin. The active tension (y-axis) is plotted against the Log concentrations (x-axis). There was no significant change in active tension at any concentration of the drug. N is number of samples and P is number of patients from who tissue was collected.

Digoxin, however, produced neither any significant vasodilation nor any vasoconstriction at any concentration. The EC_{50} was not calculated as there was no significant effect on the PA rings.

4. Discussion

The primary objective of our experiment was to evaluate the *ex vivo* effects of amiodarone and digoxin on human pulmonary arterial tension and thereby qualify if they may be safe to use when treating patients with post-operative arrhythmias and concomitant PH.

Amiodarone has long been proven to be an effective therapy that can subdue ventricular arrhythmias and improve ventricular function [24]. It also has proven vasodilatory effects in coronary and peripheral circulation that can help to improve myocardial perfusion and reduce systemic blood pressure and afterload [22]. It is apparent from our experiments that amiodarone's vasodilatory effects may extend even to the context of PH based on the outcomes of our experiments.

Amiodarone's positive impact on myocardial perfusion and coronary blood flow gives it a role in the specialist treatment of chronic heart failure, especially when uncontrolled with other medication [25]. Ventricular failure is a common accompanying symptom of severe secondary PH. Therefore, if the effects of amiodarone on pulmonary arterial tension can be evaluated and shows significant promise, it can be used to effectively manage complications in patients with right ventricular dysfunction. Moreover, amiodarone has been shown to be more effective than some beta-blockers in reducing incidence of POAF and was associated with shorter hospital stays [13].

Although it is a very effective treatment, long-term amiodarone therapy can be associated with very serious side effects. Amiodarone-induced pulmonary toxicity is an umbrella term for a range of disorders that can manifest as pneumonitis, pneumonia, acute respiratory distress syndrome, and other potentially life-threatening complications [26]. However, the results of our study warrant further investigation into amiodarone's role in PH.

Digoxin on the other hand had no significant vasodilatory effects on the PA rings. There were also no significant vasoconstrictive effects displayed. The lack of any obvious vasoconstriction could mean that it may be safe to use in patients with PH. Digoxin, unfortunately, also has an infamously narrow therapeutic index which means that it often leads to toxicity. Digoxin toxicity usually manifests as cardiac symptoms such as bradycardia and AV block. Extracardiac signs include gastrointestinal upset and vision disturbances [27].

It is important to correlate our findings to clinical situations to understand their relevance. We can do so by comparing the data to plasma concentrations of the drugs when used clinically. Amiodarone is said to have a therapeutic concentration around 2 μg/mL (1.5–2.5 μg/mL) which is approximately equivalent to 3 μM [28]. At this concentration, the active tension of vessel under amiodarone was −0.127 gf (±0.064) in our experiments. Based on our results, we can hypothesize that amiodarone will not have vasoconstrictor effects at clinically utilized therapeutic levels. A comprehensive study by Goldberger and Goldberger suggests that digoxin should have a therapeutic target of 0.8 ng/mL which is approximately equivalent to 1 pM [29]. At this concentration, vessels under digoxin had an active tension of 0.022 gf (±0.008). Based on our results, this could mean that digoxin could cause minor vasoconstriction in patients.

One limitation of our study was that our experiments used arterial tissue from patients who did not have PH. We aimed to minimize the impact of this using PGF2α to pre-constrict the vessel which mimics the mechanism of prostaglandin-mediated vasoconstriction seen in PH [30]. *In vivo* pathophysiology of increased pressure in PH is much more complex, however, and not feasibly reproducible in lab conditions. Moreover, there was some heterogeneity between tissue samples in the change in vessel tension after addition of PGF2α. Hence, this could mean that the pharmacodynamics of subsequent addition of therapeutics could also vary. However, none of the samples exhibited constrictor effects secondary to the antiarrhythmics, so this disparity is not concerning and does not invalidate the conclusion regarding the safety of these agents.

Another consideration we need to keep in mind was that our experimental set up used an additive model which means the

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effects were the result of gradual build-up of the drugs in the arterial tissue. Hence, this may mean that the potential vasodilatory benefits of amiodarone may not be immediately visible but may rather be the result of continued drug use.

In essence, our study was the first to examine the effects of AADs on human pulmonary arterial tension as a preliminary step to determine the safety profile of these drugs in patients with PH. The roles of other drugs such as beta-blockers and calcium channel blockers in this specific patient subset are very unclear in POAF without PH. Therefore, future trials we conduct should focus on clarifying the role of other AADs in this patient group. Their effectiveness in patients without PH is well-known and confirmation of their safety profile and efficacy in PH could provide more options for treatment with the possibility of avoiding serious pulmonary complications such as those caused by amiodarone and the dangerous cardiotoxic effects of digoxin.

5. Conclusions

Although there is bountiful evidence to support the use of amiodarone and digoxin in post-operative arrhythmias, there is very limited evidence regarding the safety of these drugs in the presence of PH. This is the first experiment to evaluate the effect of these drugs on human pulmonary arterial tension. Preliminary experiments have shown promising results in terms of the vasoactive effects of amiodarone. If this is consistent with future experiments, further, clinical trials can be run to test the efficacy of amiodarone against existing treatments of PH.

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Conflicts of Interest

None declared.

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