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Beta-blockers in non-surgical patients with type A aortic dissection

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A B S T R A C T

Type A aortic dissection (TAAD) is a catastrophic condition with 24–48% mortality during the first day, if patients are not surgically treated. Due to old age and associated co-morbidities surgeons may be reluctant to operate and patients are administered medical therapy for the end of reducing systolic blood pressure and heart rate. Beta-blockers (BB) are the "medications of choice". Based on physical and physiological considerations, it was hypothesized that BB may actually exacerbate TAAD.

Aortic dissection – the medical challenge

An 86 year old lady was admitted to internal medicine complaining of acute severe chest pain radiating to her back, in-between scapulae. CT angiography demonstrated type A aortic dissection (TAAD) (Stanford classification) which is associated with high mortality (approximately 1–2% mortality per hour for the first 24 h) if not surgically treated [1]. Considering her age and risk factors surgeons were reluctant to operate, claiming high risk due to surgery-associated mortality. Medical therapy was instituted pursuing systolic blood pressure < 120 mmHg and heart rate (HR) < 60 beats per minute (bpm) [2–4]. As beta-blockers (BB) are the "medications of choice" [5,6], and patient's HR was 90 bpm, metoprolol dose was increased from 100 mg daily to 100 mg twice daily. To note, scanty literature regarding the efficiency of medical treatment in TAAD is available [6]. In a retrospective study, Suzuki et al. summarized that BB were associated with improved survival in patients with TAAD [6]. The goal of this communication is to challenge the role of BB as medical treatment in TAAD based on physical rationale.

Pathophysiology of aortic dissection

A tear in the intima of the ascending aorta is the initial pathology leading to TAAD. The tear serves as an orifice (AD orifice, ADO) through which blood can potentially enter and dissect the inner layers of the vessel. However, to further dissect, the pressure at the ADO must be greater than that in the deeper layers.

Factors affecting pressure at the orifice of aortic dissection

Blood pressure and flow in the aorta are best described by a resistor-capacitor in parallel (RCP) circuit model [7], which is also not complete as it does not deal with the effect of pulse wave reflection from arterial branches stemming from the aorta (discussed below).

In the RCP model, at time equal zero, when the circuit is closed and current is allowed to flow, current flows from the battery to the capacitor and resistor. The impedance on the resistor is greater than that on the capacitor and current flows to charge the capacitor. As charge accumulates on the capacitor the resistance to further charging increases and current flows through the resistor. A similar process occurs in the aorta. During systolic ejection, blood (stroke volume, SV, analogue of electric current), is delivered to the aorta. According to the compliance of the aorta (C_{aor}), the capacitance of the aorta, blood either stretches (charges) the aorta or flows downstream against systemic vascular resistance (analogue of resistor). When SV has been delivered and aortic valve closes (capacitor can no longer be charged), SV is propelled to body tissues.

The pressure in the ascending aorta is lowest during diastole and increases during systole. Aortic pressure depends on: 1. ejected SV, 2. aortic pressure prior to ejection, 3. C_{aor}, 4. systemic vascular resistance and 5. Pulse wave reflection. Briefly, pulse wave is a mechanical perturbation, created during ejection, which travels through vessel wall from the heart to the periphery. Part of the perturbation is reflected backwards (to the heart) from vessel bifurcations. The "returning" wave may coincide with the forward travelling wave creating a constructive interference. The latter increases central pressure measured at the ascending aorta, resulting in increased pressure affecting the ADO [8]. It has been shown that constructive interference occurs at lower heart rates [8].

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Hypothesis: beta blockers may actually increase the pressure in the ascending aorta

BB produce their hemodynamic effects with relation to the ambient degree of beta receptor stimulation [9]. Adrenergic stimulation increases: inotropism (contractility), chronotropism (HR), lusitropism (rate of myocardial relaxation), and dromotropism (rate of impulse conduction). All BB antagonize adrenergic stimulation. When ambient beta stimulation is low, BB exert minimal effects [9]. In TAAD the level of adrenergic stress is high due to pain (chest or back), stress of hospitalization, and mental stress associated with the impending severe complications [4].

We searched early literature investigating the hemodynamic effects of BB in general and metoprolol in particular (as a representative of the cardioselective BB) in order to learn the differential effects of BB on HR and contractility. Literature search did not provide a clear ratio between negative chronotropic and inotropic effects of BB. It is our notion that studies reported a negative chronotropic effect accounting for the decrease in inotropism and cardiac output (CO) [10,11].

Consider an isolated negative chronotropic effect. Let HR = HR1 prior to BB administration, and HR = HR2 (with the BB effect). HR2 = k*HR1 (and $k < 1$). Assume CO is determined by body tissues needs and maintained by physiological feedback mechanisms, where CO = HR·SV. Thus, for HR1, SV = SV1, and for HR2, SV = SV2, where SV2 = SV1/k. Thus, when HR is slowed by BB the resultant SV is increased. According to the relation $C_{aor} = \Delta V/\Delta P$, where ΔV is the instantaneous ejected volume and ΔP is the resulting increase in aortic pressure, the greater the ejected SV (ΔV), the greater is the pressure increase at the ADO. In addition, at a greater initial volume of the ascending aorta, C_{aor} decreases [7]. This fact translates into further increase in aortic pressure. Per patient it is difficult to evaluate whether backward and forward travelling pulse waves interfere constructively or destructively. Dart et al. reported that aortic pressure is amplified at lower HRs [8–12]. In support of that, Goldberger et al. showed an inverse relation between blood pressure and HR in humans [13]. To conclude, based on the above reasoning, it would be preferred to avoid slowing HR, as this: 1. increases SV, resulting in a greater aortic pressure, 2. forces the aorta to operate at a lower value of C_{aor}, and 3. may set the conditions for constructive interference, which may further increase the pressure at the ADO.

Consider an isolated negative inotropic effect. In this case, decreased contractility would cause a decrease in SV and CO, which may be well tolerated, if lower limit of CO is not exceeded. Such an effect is favorable (a smaller SV results in a smaller increase of pressure in the ascending aorta and also allows the aorta to operate at a higher value of C_{aor}), however, we did not find references describing an isolated inotropic effect of BB.

Consider the case of mixed negative inotropic and chronotropic effect, where both SV and HR are similarly decreased. Such an effect may be less efficient, as the decrease in HR may be counteracted by a prolonged diastole allowing for a greater LV filling (thus increasing SV once again).

Conclusion

It is clear that lowering ascending aortic pressure is a therapeutic goal in non-surgical TAAD patients. The proposed physical/physiological reasoning shows that BB have the potential to increase the pressure at the ADO and exacerbate TAAD. This hypothesis should be examined in a hemodynamic lab where central pressure measurement is available.

Declaration of Competing Interest

Authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.05.008.

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