SUPPLEMENTAL MATERIAL

Physiology of angina and its alleviation with nitroglycerine – insights from invasive catheter laboratory measurements during exercise

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Short Title: *Asrress et al*: Nitroglycerine in exercise-induced angina

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Supplement Methods

Wave intensity represents the rate of energy per unit area transported by travelling waves in arteries and is derived from phasic changes in local pressure and flow velocity.[1] In the coronary circulation backward travelling waves are generated distally by cardiac contraction and relaxation at the downstream end, and forward travelling waves arise from changes in aortic pressure at the inlet.[2-4] Therefore, in the coronary circulation Wave Intensity Analysis (WIA) reflects the interactive effects of cardiac mechanics and coronary conductance on coronary haemodynamics.[3,5-7] A typical sequence of waves generated during the cardiac cycle is shown in **Online Figure 1**. The first is a backward compression wave (BCW) an early decelerating pressure wave in early systole during isovolumic contraction. The backward expansion wave (BEW) is an accelerating pressure wave that occurs in early diastolic relaxation at the highest diastolic aortic pressure and max diastolic flow, which is proposed as being the dominant energy in diastole responsible for 'sucking' blood into the microvascular space. The forward waves are related to changes in aortic pressure, the most dominant being the forward compression wave (FCW), a systolic pressure wave that accelerates a very low level mid-systolic flow at peak aortic pressure after isovolumic contraction arising from the increasing proximal pressure as the aortic valve opens.

WIA was performed with custom software (CardiacWaves, King's College London, UK), using methodology previously described.[4,6] The distal pressure and velocity signals were smoothed with a Savitzky-Golay filter to reduce signal noise [8] and were adjusted to correct for the time delay between the digitally archived pressure and velocity signals (55 ms). The energy carried by the 3 most prominent identified waves, FCW, BCW, BEW, were analyzed and included in this article, and were obtained by the area under the wave and normalized for the sampling interval. The investigators who performed the data analyses were blinded to all of the clinical patient data.

Supplemental Results

The wave intensity during the study protocol is summarized in **Online Figure 2**. Although both the FCW and BCW appear to increase during exercise, the changes are not statistically significant. The BEW increases significantly during exercise (*P*=0.0174 Base to Peak; *P*=0.0018 Base to +2min post GTN). At 2 minutes post peak exercise there was a fall in BEW in the Control group which was not seen in the GTN group (*P*=0.0260).

Supplemental Discussion

The mechanisms of action of GTN have been summarised in the main manuscript. It was felt that the WIA did not provide any additional insight beyond the clear mechanisms already presented. The results are presented here for completeness. Clear changes to coronary geometry have been demonstrated in the main manuscript. WIA has been developed and studied in situations where vessel geometry does not change (certainly intentionally). Although the wave intensity measured at that particular position in the coronary artery is valid, the wider energetics associated with some of the changes in geometry are less clear. This therefore limits the conclusions that can be reached from this analysis, however the mechanisms identified here, are nevertheless hypothesis generating.

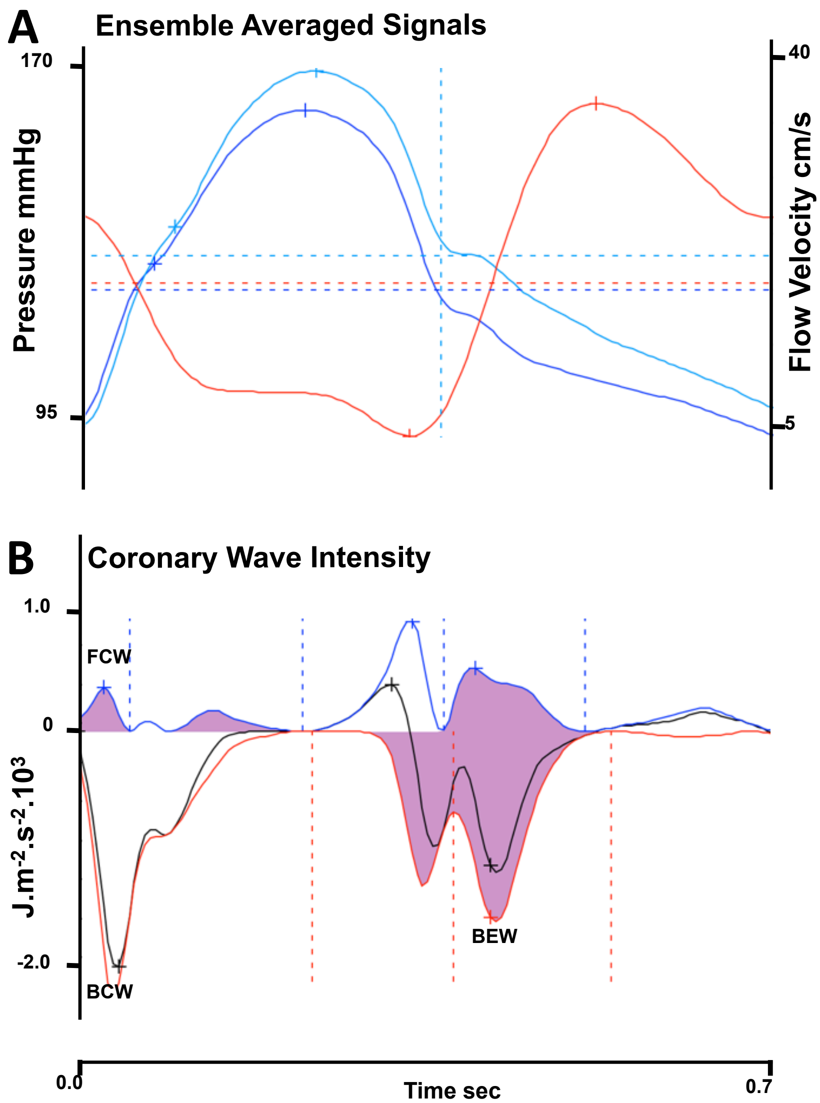
A possible mechanism to aide myocardial perfusion is the effects of microcirculatory suction, which occurs during diastolic relaxation. This is an active processes requiring oxygen. As ischemia has been shown to attenuate diastolic relaxation,[9] we can hypothesise that during ischemia the ability to generate microcirculatory suction is diminished. This is supported by our data where BEW reduced sequentially following peak exercise conditions in the Control group, whereas this is maintained with GTN administration. This is consistent with work by Amende and Fujimoto that showed that nitroglycerine, in the resting state, increased the speed of isovolumic relaxation and improved diastolic function.[10-12]

Supplemental Conclusion

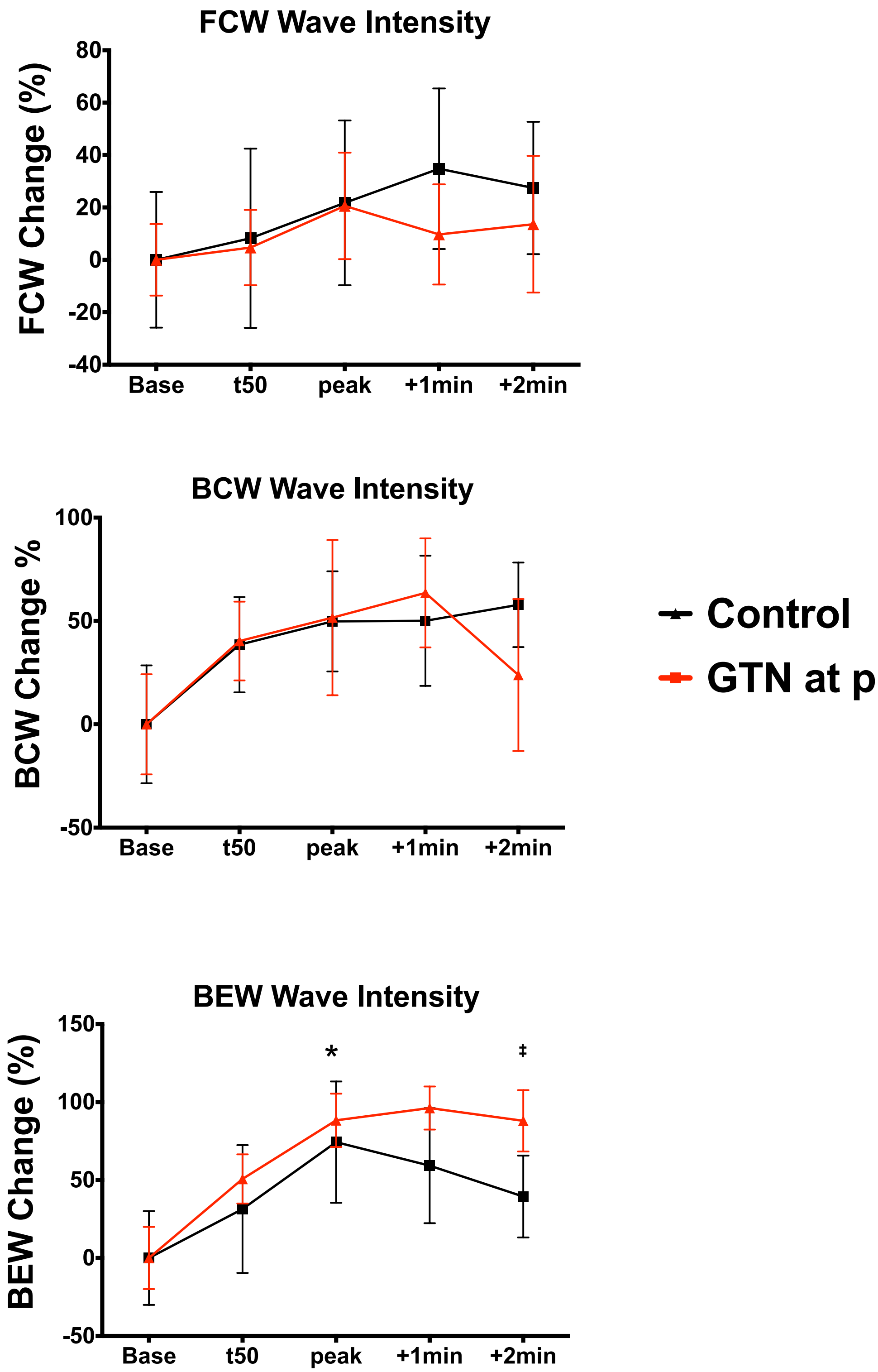
Exercising beyond ischemia causes a reduction in microcirculatory suction likely due to diastolic dysfunction. Administration of GTN results in maintenance of microcirculatory suction which, together with the mechanisms demonstrated in the main manuscript, contributes to the alleviation of angina.

Supplemental Figures

Supplemental Figure 1: Coronary Pressure, Flow and Wave Intensity



Supplemental Figure 2: Coronary Wave Intensity Analysis



Supplemental Figure Legends

Supplemental Figure 1: Coronary Pressure, Flow and Wave Intensity. A: Coronary pressure (Aortic light blue, distal coronary dark blue line) and flow velocity measurements (red line). B: Calculated wave intensity. The black line outlines the net energies, with the red and blue showing the separated waves. FCW = Forward Compression Wave; BCW – Backward Compression Wave; BEW = Backward Expansion Wave.

Supplemental Figure 2: Coronary Wave Intensity Analysis. FCW = Forward Compression Wave; BCW – Backward Compression Wave; BEW = Backward Expansion Wave. *=statistically significant difference Base vs peak exercise (peak), P<0.05, [‡]=statistical significant difference at +2min control vs GTN group.

Supplemental References

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