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TNF-α Mediated β1 Integrin Inactivation is a Novel Mechanism Mediating Left Ventricular Dilatation

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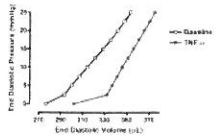
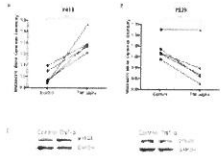
OBJECTIVE: We previously reported that β1 integrin-mediated adhesion of cardiac myocytes to components of the extracellular matrix (ECM) is significantly reduced in the aortocaval fistula model of chronic volume overload. Other studies have shown that myocardial TNF-α is significantly elevated in this model. Therefore, this study sought to test the hypothesis that pathophysiologic levels of TNF-α produce ventricular dilatation by significantly reducing integrin-mediated adhesion of cardiomyocytes to the ECM. METHODS: To this end, adult male Sprague-Dawley rats (n=10) were continuously infused with TNF-α (2.5 μg/kg/hr) via subcutaneously implanted osmotic minipumps (Alzet model 2002, Alza Corp, Mountain View, CA) for 3 days. This rate of infusion resulted in systemic levels of biologically active TNF-α of 17 ± 6.3 pg/ml of serum, which is comparable to that reported in patients with heart failure. Calcium tolerant cardiomyocytes were isolated from the TNF-α infused rat hearts by perfusion with Joklik's MEM solution containing Type II collagenase (Worthington Biochemical Corp., Lakewood, NJ). The adhesion of these cardiomyocytes to laminin were compared to cardiomyocytes from a separate, age-matched control group (n=7). The adhesion assay was carried out in 24-well culture plates coated with laminin (Becton-Dickinson; Bedford, MA) incubated at room temperature for 1 hr. In a subsequent study the effect of a continuous TNF-α infusion on the left ventricular pressure-volume relationships in normal hearts (n=3) was determined using a blood perfused Langendorff isolated heart preparation prior to (baseline) and 30 minutes after initiating the TNF-α infusion. Western blots were performed with primary antibodies directed against phosphospecific Src kinase tyrosine residues (pY418) and (pY529). RESULTS: Cardiomyocyte adhesion to laminin in the TNF-α infused rats was significantly decreased relative to the untreated controls (27.1 ± 3.2% vs 40.3 ± 3.0%, respectively; $p<0.05$). As can be seen in Figure 1, perfusion with TNF-α produced rapid left ventricular dilatation comparable to that previously reported after β1 integrin inactivation. The significant right shift in the pressure-volume relationship induced by TNF-α reflects the rapid development of ventricular dilatation. Figure 2 demonstrates TNF-α infusion produces contrasting effects of significant tyrosine Y418 phosphorylation (Panel A) and dephosphorylation of tyrosine Y529. CONCLUSION: TNF-α produces a marked decrease in adult cardiomyocyte adhesion to the ECM; and TNF-α mediates acute alterations in integrin-mediated cardiomyocyte adhesion which involves Src kinase-mediated integrin inactivation. These finding implicate an acute TNF-α induced reduction in cardiomyocyte integrin function as a novel mechanism contributing to ventricular dilatation. TNF-α mediated changes in mechanotransduction also represent a likely mechanism responsible for gender differences in cardiomyocyte remodeling previously reported in the aortocaval fistula model.



The significant right shift induced by TNF-α reflects the acute development of significant left ventricular dilatation.



TNF-α infusion produced contrasting effects on myocardial Src kinase, with significant tyrosine Y418 phosphorylation (Panel A) and dephosphorylation of tyrosine Y529 (Panel B) residues in Src kinase.

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