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Heart failure is a progressive weakening of heart muscle leading to death. Studies in animals have shown that heart failure is a result of reduced cardiac muscle contraction that appears to be caused by changes in phosphorylation at several sites of contractile proteins. However, the precise location and degree of phosphorylation of these proteins remain poorly understood. Traditional biochemical methods lack both the speed and sensitivity to identify and quantify site-specific phosphorylation in contractile proteins in small biopsies obtained from human hearts, and thus, approaches with high efficiency and sensitivity, such as mass spectrometry, are required. Previs *et al.* (2008) developed a global mass spectrometry data gathering method to quantify site-specific phosphorylation in contractile proteins, but the method (1) uses 1-D gel separation of the component proteins that limits the number of heart samples that can be analyzed and (2) had poor analytic precision to measure phosphorylation. We have developed a novel mass spectrometry-based proteomic method to address these limitations. First, we have developed a sample preparation method to selectively purify cardiac contractile proteins from heart tissue, circumventing use of a 1-D gel separation of the component proteins. Second, we have developed a focused mass spectrometry analysis and data collection scheme to selectively measure phosphorylation sites of interest. We demonstrate the method in failing and non-failing hearts obtained from mice.