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Little is known about the contribution of C-afferent fibres to chronic painful conditions in humans. We sought to investigate the role of C-fibres in the pathophysiology of pain and hyperalgesia in erythromelalgia as a model disease for chronic pain. Erythromelalgia is a condition characterized by painful, red and hot extremities, and patients often report tenderness on walking. We made microneurographic recordings from single C-fibres in cutaneous fascicles of the peroneal nerve in patients suffering from this disease. All patients had had a pain attack recently and psychophysical signs of allodynia and punctate hyperalgesia were found. We obtained recordings from a total of 103 C-fibres and found significantly lower conduction velocities and increased activity-dependent slowing of the conduction velocity of afferent C-fibres in the patients compared with healthy controls. Furthermore, several units with biophysical properties of mechano-insensitive fibres were pathological, being spontaneously active or sensitized to mechanical stimuli. Since these fibres also mediate the axon reflex flare, their hyperexcitability might account not only for ongoing pain and tenderness but also for redness and warming in this pain syndrome. The changes in conductive properties found in the C-fibres of these patients could be the first signs of a small-fibre neuropathy. This is the first systematic study of single C-fibres in patients and it shows an active contribution of mechano-insensitive fibres to chronic pain.